Lipotropics, Other
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Agents in this class are indicated as adjuncts to dietary modifications for the treatment of various dyslipidemias.

Drug	Manufacturer	Indication(s)
Apolipoprotein B Synthesis Inhibitors		
lomitapide (Juxtapid®)[1]	Aegerion	Reduction of LDL-C, total cholesterol, apolipoprotein B (Apo B), and non-HDL-C in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to a low-fat diet and other lipid-lowering treatments
mipomersen (Kynamro®)[2]	Genzyme	Reduction of LDL-C, total cholesterol, apolipoprotein B (Apo B), and non-HDL-C in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to diet and lipid-lowering medications
Bile Acid Sequestrants		
cholestyramine (Questran)[3]	generic	▪ Primary hypercholesterolemia ▪ Relief of pruritus associated with partial biliary obstruction
colesevelam (WelChol®)[4]	Daiichi Sankyo	▪ Hypercholesterolemia, Fredrickson type IIa (monotherapy or in combination with a statin) ▪ Reduction of LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) after failing an adequate trial of diet therapy ▪ Glycemic control in adults with type 2 diabetes mellitus
colestipol (Colestid®)[5]	Pfizer, generic	▪ Primary hypercholesterolemia
Cholesterol Absorption Inhibitors		
ezetimibe (Zetia®)[6]	Merck Sharp & Dohme	▪ Primary hypercholesterolemia (monotherapy or in combination with a statin) ▪ Mixed hyperlipidemia (in combination with fenofibrate) ▪ Homozygous familial hypercholesterolemia (HoFH) (adjunctive therapy in combination with atorvastatin or simvastatin) ▪ Homozygous familial sitosterolemia
Fibric Acids		
fenofibrate (Antara®)[7]	Lupin, generic	▪ Primary hypercholesterolemia or mixed dyslipidemia, Fredrickson types IIa and IIb ▪ Hypertriglyceridemia, Fredrickson types IV and V hyperlipidemia
fenofibrate (Fenoglide®)[8]	Santarus, generic	
fenofibrate (Lipofen®)[9]	Kowa, generic	
fenofibrate (Lofibra®)[10]	generic	
fenofibrate (Tricor®)[11]	Abbvie, generic	
fenofibrate (Triglide®)[12]	Shionogi	
fenofibric acid (Fibricor®)[13]	Caraco, generic	▪ Primary hyperlipidemia or mixed dyslipidemia ▪ Severe hypertriglyceridemia (≥ 500 mg/dL)
fenofibric acid (Trilipix®)[14]*	Abbvie, generic	▪ Primary hyperlipidemia or mixed dyslipidemia ▪ Severe hypertriglyceridemia
gemfibrozil (Lopid®)[15]	Pfizer, generic	▪ Hypercholesterolemia, Fredrickson type IIb (in patients without history of or symptoms of existing CHD) ▪ Hypertriglyceridemia, Fredrickson types IV and V hyperlipidemia

FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)
Niacin		
niacin ER (Niaspan®)[16]**	Abbvie, generic	▪ Primary hyperlipidemia or mixed dyslipidemia ▪ Primary hyperlipidemia or patients with a history of Coronary Artery Disease (CAD) and hyperlipidemia (in combination with a bile acid sequestrant) ▪ Severe hypertriglyceridemia as adjunct in patients at risk for pancreatitis ▪ Patients with a history of myocardial infarction (MI) and hyperlipidemia
niacin IR (Niacor®)[17]	Upsher-Smith	▪ Primary hypercholesterolemia (monotherapy or in combination with bile-acid binding resin) ▪ Hypertriglyceridemia, types IV and V hyperlipidemia for those who present with a risk of pancreatitis (adjunctive therapy)
Omega-3 Fatty Acids		
icosapent ethyl (Vascepa®)[18]	Amarin	▪ Treatment of hypertriglyceridemia in adults with severe triglycerides (TG) ≥ 500 mg/dL, as adjunct to diet.
omega-3-acid ethyl esters (Lovaza®)[19]	GlaxoSmithKline, generic	▪ Treatment of hypertriglyceridemia in adults with triglycerides (TG) ≥ 500 mg/dL
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors		
alirocumab (Praluent®)[20]	Sanofi-Aventis	▪ Treatment of adults with HeFH or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of LDL-C as an adjunct to diet and maximally-tolerated statin therapy
evolocumab (Repatha™)[21]	Amgen	▪ Treatment of adults with HeFH or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of LDL-C as an adjunct to diet and maximally-tolerated statin therapy ▪ Treatment of patients with HoFH who require additional lowering of LDL-C as an adjunct to diet and other LDL-lowering therapies

The effects of icosapent ethyl and omega-3-acid ethyl esters on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia have not been determined. The effect of icosapent ethyl and omega-3-acid ethyl esters on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined.

The effect of lomitapide or mipomersen on cardiovascular morbidity and mortality has not been determined. The safety and effectiveness of lomitapide or mipomersen have not been established in patients with hypercholesterolemia who do not have HoFH.

The use of mipomersen as an adjunct to LDL-C apheresis is not recommended.

*In April 2015, the FDA removed the indication for Trilipix as an adjunct to diet in combination with a statin to reduce triglycerides and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal.

**In April 2015, the FDA removed the indication for Niaspan in combination with simvastatin or lovastatin for the treatment of primary hyperlipidemia and mixed dyslipidemia when treatment with Niaspan, simvastatin, or lovastatin monotherapy is considered inadequate.

OVERVIEW

Many clinical trials have demonstrated that a high serum concentration of low-density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C) are major risk factors for coronary heart disease (CHD). The National Health and Nutrition Examination Survey (NHANES) reported that in 2011-2014 approximately 12.1% of adults aged 20 years and over had high total cholesterol (≥ 240 mg/dL) and 18.5% had low HDL-C (< 40 mg/dL); the incidence being higher in women (13%) compared to men (10.6%).[22] Also, high total cholesterol levels are reported more frequently in Hispanic adults compared to non-Hispanic adults. The NHANES analysis was based on measured cholesterol only and does not take into account whether lipid-lowering medications were taken. In addition, NHANES reported that the percentage of adults aged 20 and over with elevated triglycerides declined from 33.3% for 2001-2004 to 25.1% during 2009-2012.[23] In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA), in combination with the National Heart, Lung, and Blood Institute (NHLBI), released 4 new consensus guidelines regarding cholesterol management, cardiovascular (CV) risk assessment, obesity, and lifestyle. ACC/AHA emphasizes lifestyle modification, including a reduced calorie diet and aerobic physical activity, as a critical component of atherosclerotic cardiovascular disease (ASCVD) risk reduction, both prior to and in conjunction with cholesterol lowering drug therapies.[24,25,26,27]

There is a high level of evidence supporting the use of hydroxymethyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors ("statins") for secondary prevention and moderate to high level of evidence for their use for primary prevention.[28] As a class, they can lower LDL-C by up to 60% in a dose-related fashion. Statins typically have relatively minor effects on triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C), reducing TG by 6% to 30% and increasing HDL-C by 2% to 16%.

Many non-statin therapies do not provide adequate ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD.[29] As demonstrated in the AIM-HIGH study, the additional reduction in non-HDL–C (as well as apolipoprotein B [Apo B], lipoprotein (a) [Lp(a)], and triglycerides) levels with niacin therapy did not further reduce ASCVD risk in individuals treated to LDL–C levels of 40 to 80 mg/dL. The ACCORD trial reported that, in patients with and without clinical CV disease, the addition of a fenofibrate to simvastatin therapy did not reduce the risk for CV events compared with simvastatin alone. However, ACC/AHA recognizes that maximal statin therapy might not be adequate to lower LDL–C sufficiently to reduce ASCVD event risk in individuals with primary severe elevations of LDL–C at which time the addition of non-statin agents can be considered. In contrast, the IMPROVE-IT study reported an average additional reduction in LDL-C of 17 mg/dL with the addition of ezetimibe to simvastatin.[30] The primary composite endpoint of CV death, myocardial infarction (MI), unstable angina, stroke, and coronary revascularization was significantly lower with combination therapy as compared to simvastatin alone (32.7% versus 34.7%, respectively; p=0.016). A significant reduction in MI and ischemic stroke and a nonsignificant increase in risk of hemorrhagic stroke were also reported with combination therapy.

ACC/AHA no longer supports the use of the National Cholesterol Education Program (NCEP) Expert Panel on Diagnosis, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) algorithm for risk assessment citing that it is derived in an exclusively white sample population and the limited scope of the outcomes in determining CHD alone.[31] Instead, they recommend use of the new race- and gender-specific Pooled Cohort Equations to estimate 10-year ASCVD risk in both white and black men and women.[32] They also no longer support a treat-to-target approach with goals such as LDL–C <

70 mg/dL and < 100 mg/dL for secondary and primary ASCVD prevention, respectively; rather, the guidelines advocate using the maximum tolerated statin intensity in patients identified to benefit from statin therapy.[33] This guideline focuses on treatments proven to reduce ASCVD events and is not intended to be a comprehensive approach to lipid management. ACC/AHA also suggests the use of non-HDL-C, apo B, lipoprotein-a, or LDL particles in guiding treatment decisions. Routine use of carotid intima media thickness (CIMT) is no longer recommended by the ACC/AHA; it should only be used as a research tool.

High plasma HDL cholesterol (HDL-C) is associated with reduced risk of MI, but whether this association is causal is unclear. A study published in 2012 that utilizes databases of genetic information has found that raising HDL-C levels may not affect heart disease risk.[34] The study reported that carriers of the *LIPG* 396Ser allele (2.6% frequency) had higher HDL-C (0.14 mmol/L higher; $p=8\times10^{-13}$) but similar levels of other lipid and non-lipid risk factors for MI compared with non-carriers. This difference in HDL-C was expected to decrease risk of MI by 13% (odds ratio [OR], 0.87; 95% CI, 0.84 to 0.91), but the investigators found that the 396Ser allele was not associated with risk of MI (OR, 0.99; 95% CI, 0.88 to 1.11; p=0.85). These data challenge the concept that raising HDL-C will uniformly translate into reductions in risk of MI.

NCEP categorizes above normal serum triglyceride levels as borderline high with levels between 150 to 199 mg/dL; high triglycerides between 200 to 499 mg/dL, and very high as levels 500 mg/dL or above.[35] The 2012 guidelines on the evaluation and treatment of hypertriglyceridemia by the Endocrine Society (ES) state that severe and very severe hypertriglyceridemia increase the risk for pancreatitis, whereas mild or moderate hypertriglyceridemia may be a risk factor for CVD. To take into account the risk for pancreatitis, the ES defines mild hypertriglyceridemia as triglyceride levels between 150 to 199 mg/dL; moderate hypertriglyceridemia as levels between 200 to 999 mg/dL, severe hypertriglyceridemia as triglyceride levels between 1,000 to 1,999 mg/dL, and very severe hypertriglyceridemia as triglyceride levels 2,000 mg/dL or greater. A high triglyceride level is a component of metabolic syndrome, which is associated with risk for CVD.[36] The ES recommends hypertriglyceridemia screening in adults as part of a lipid panel at least every 5 years and suggests that use of apoB or Lp(a) levels can be of value. Patients with primary hypertriglyceridemia should be evaluated for family history of dyslipidemia and CVD to assess genetic causes and future CVD risk. In addition to lifestyle changes, ES recommends drug therapy to reduce the risk of pancreatitis in patients with severe and very severe hypertriglyceridemia; a fibrate is considered first-line treatment. For patients with moderate to severe hypertriglyceridemia, fibrates, niacin, and omega-3 fatty acids alone or in combination with statins may be considered. Statins should not be used alone for severe or very severe hypertriglyceridemia; however, statins may be useful for the treatment of moderate hypertriglyceridemia to modify CVD risk. Recommended treatment goals for patients with moderate hypertriglyceridemia are non-HDL-C < 130 mg/dL in patients with CHD or a CHD Risk Equivalent (10-year risk for CHD > 20%), non-HDL-C < 160 mg/dL in patients with at least 2 risk factors, and non-HDL-C < 190 mg/dL in those with 0 to 1 risk factor.[37]

Studies to date have not demonstrated an overall benefit of fibrates for reduction of CV events or total mortality; although post-hoc subgroup analyses have reported a decrease in composite CV events with the use of fibrates in patients with moderate hypertriglyceridemia.[38] In addition, no studies using high-dose omega-3 fatty acids in patients with hypertriglyceridemia have shown a beneficial CV outcome.

In 2012, the American Association of Clinical Endocrinologists (AACE) published guidelines for the management of dyslipidemia and prevention of atherosclerosis. [39] AACE also includes lipid screening in the pediatric populations and recommend that children older than 2 years and adolescents older than

16 years be evaluated every 3 to 5 years and every 5 years, respectively, if they have CAD risk factors or a family history of premature CAD or dyslipidemia. AACE supports the use of apo B in evaluating lipids and recommends an optimal apo B < 90 mg/dL for patients at risk of CAD, while patients with established CAD or diabetes who have one or more additional risk factors should have an apo B < 80 mg/dL. They recommend fibrates for treatment of TG > 500 mg/dL. Niacin can be used for reducing TG, increasing HDL-C, and reducing LDL-C. Omega-3 fish oil (2 g to 4 g) can be used, as adjunct to fibrates or niacin if necessary, to achieve satisfactory triglyceride lowering. AACE recommends bile acid sequestrants for reducing LDL-C and apo B and modestly increasing HDL-C, but these agents may increase triglycerides. Cholesterol absorption inhibitors are effective as monotherapy in reducing LDL-C and apo B. In addition, combination therapy with statins can be used. AACE recommends pharmacotherapy for children and adolescents older than 8 years who do not respond sufficiently to lifestyle modification and particularly for those with either LDL-C ≥ 190 mg/dL or LDL-C ≥ 160 mg/dL and the presence of 2 or more CV risk factors, or a family history of premature CAD. These guidelines also address the unique challenges associated with atherosclerosis and heart disease in women. They recommend the following pharmacotherapy for all women at high risk: lipid-lowering pharmacotherapy (preferably with a statin) regardless of LDL-C level, and niacin or fibrate therapy in the presence of low HDL-C or elevated non–HDL-C; for all women at intermediate risk: lipid-lowering pharmacotherapy (preferably with a statin) in the presence of an LDL-C level greater than 130 mg/dL, and niacin or fibrate therapy in the presence of low HDL-C or elevated non–HDL-C after LDL-C goal is reached.

In 2015 the AHA/American Diabetes Association (ADA) released updated guidelines on CVD prevention in patients with type 2 diabetes.[40] This scientific statement provides recommendations from the review of current literature and clinical trials related to the control of blood pressure, blood glucose, and cholesterol. Emphasis is placed on lifestyle and CVD risk factor management. As they are joint guidelines between the AHA and ADA, they reflect the AHA guidelines discussed above. Specifically, they recommend a moderate intensity statin for diabetic patients aged 40 to 75 years with an LDL-C of 70 mg/dL to 189 mg/dL and a high intensity statin for diabetic patients aged 40 to 75 years with at least 7.5% estimated risk of ASCVD. The guidelines further state that practitioners should evaluate the benefit of statin treatment in patients who fall outside of the 40 to 75 year age range. They also recommend evaluation and treatment in patients with fasting TG > 500 mg/dL.

The Fredrickson classification was adopted by the World Health Organization (WHO) and categorized dyslipidemias by patterns of elevation in lipids and lipoproteins.[41] Type I is characterized by elevated chylomicrons and triglycerides (TGs); type IIa by elevated LDL and cholesterol; type IIb by elevated LDL, very low density lipoprotein cholesterol (VLDL-C), TGs and cholesterol; type III by elevated VLDL, chylomicron remnants, TGs, and cholesterol; type IV by elevated VLDL and TGs; and type V by elevated chylomicrons, VLDL, TGs, and cholesterol. The Fredrickson classification does not directly account for HDL, and it does not distinguish among the different genes that may play a role in dyslipidemia.

The National Lipid Association (NLA) published Parts 1 and 2 of their new recommendations for patient-centered management of dyslipidemia in 2015.[42,43] Atherosclerosis develops over decades often beginning in childhood. Targeted lipid screening should begin at 2 years of age if warranted by family history; universal screening is appropriate at ages 9 to 11 years and repeated at age 20 years. The NLA recommends using lipid levels in conjunction with other ASCVD risk factors to assess overall risk and also support the use of risk calculators, such as the ATP III Framingham Risk Score and the ACC/AHA Pooled Cohort Equations. The NLA considers non-HDL-C to be superior to LDL-C for predicting

ASCVD event risk since non-HDL-C is better correlated with apo B, and is more closely associated with the total burden of atherogenic particles. Non-HDL-C measurements are used along with LDL-C as primary targets of therapy. Triglyceride level is associated with the very low density lipoprotein cholesterol (VLDL-C) level, therefore using non-HDL-C as a target also simplifies the management of patients with high triglycerides. Desirable targets in patients with low, moderate, and high risk of ASCVD event are non-HDL-C <130 mg/dL and LDL-C <100 mg/dL; in patients considered to be at very high risk target measures are <100 mg/dL and <70 mg/dL, respectively. The NLA advises that the intensity of risk-reduction therapy should be based on the patient's absolute risk for an ASCVD event. The NLA recommends lifestyle therapies such as diet modification and moderate physical activity before initiating drug therapy for patients at low and moderate ASCVD event risk; however in patients at high or very high risk, drug therapy may be prescribed from the start. Moderate to high intensity statin therapy is considered first-line drug therapy. Non-statin agents, such as ezetimibe, bile acid sequestrants, fibric acids, long-chain omega-3 fatty acid concentrates, and nicotinic acid can be considered in patients with contraindications or intolerance to statins, or as an add-on to maximally tolerated statin therapy if cholesterol levels are still elevated with maximally tolerated statin doses. If very high triglycerides (≥ 500 mg/dL) exist, a triglyceride-lowering drug may be considered for first-line use to prevent pancreatitis. Response and adherence to therapy should be monitored every 4 to 12 months. The NLA recommends review of both cholesterol goals and adherence to therapy with patients at each visit to identify barriers or side effects; an interdisciplinary team approach should be used whenever possible. Statins remain the drug therapy of choice for those with increased cardiovascular risk conditions, including HIV/AIDS and rheumatoid arthritis, and those at risk based on ethnicity or race, such as Hispanics, African Americans and South Asians. The NLA outlines special considerations to take in to account when treating these specific patient populations.

Familial hypercholesterolemia (FH) is a genetic disorder that leads to accumulation of LDL-C particles in plasma and premature CV disease.[44,45] The more severe form, homozygous familial hypercholesterolemia (HoFH), is rare, occurring in about 1 out of a million people in the U.S. In HoFH, LDL receptor activity is nearly absent and LDL-C levels commonly range between 400 mg/dL to 1,000 mg/dL. Severe and widespread atherosclerosis affects all major arteries and children are at risk for early coronary events and valve abnormalities, particularly aortic stenosis. Historically, treating patients with HoFH has been very difficult since it is resistant to diet modifications and most medications indicated for lowering cholesterol. The less serious heterozygous familial hypercholesterolemia (HeFH) occurs in 1 in 500 persons in the U.S. CAD symptoms begin to manifest in the fourth and fifth decades of life, in men and women, respectively. Additional risk factors (e.g., genetic, metabolic, and environmental) can lead to variations in the clinical manifestations and severity of atherosclerotic disease of HeFH. Accumulation of cholesterol in nonvascular tissue (cornea, skin, tendons, and joints) also commonly occurs in children with HoFH, and in adults with HeFH.

In the 2015 Agenda for Familial Hypercholesterolemia, the AHA advises FH treatment be based on LDL-C levels, not genetic abnormality or other clinical features with an initial goal in LDL-C reduction by at least 50%.[46] This can be followed by achieving an LDL-C <100 mg/dL (absence of CAD or other major risk factors) or < 70 mg/dL (presence of CAD or other major risk factors). The maximal LDL-C reduction that can be tolerated with therapy is a practical target, particularly for higher-risk patients. Therapeutic targets for apoB and non–HDL-C have not been defined for FH. Initial drug monotherapy for those with FH includes high-intensity statin therapy (rosuvastatin or atorvastatin). If LDL-C goal is not met within 3 months of adherent therapy, ezetimibe should be added. If after another 3 months, LDL-C goal is still

not met, the addition of a PCSK9 inhibitor, a bile acid sequestrant (colesevelam), or prescription strength niacin should be considered. In most patients with HoFH, high dose statin therapy provides only modest reductions in LDL-C of 10% to 25%; however, CV and all-cause mortality has shown to occur even with modest LDL-C reduction. The addition of ezetimibe to statin therapy may provide an additional 10% to 15% LDL-C reduction. Other agents such as bile acid sequestrants, niacin, and fibrates result in only modest LDL-C–reducing effects in patients with HoFH. Four-drug combination therapy with the addition of lomitapide or mipomersen can be considered in patients with HoFH if needed. Dietary and lifestyle modifications should also be an aspect of FH treatment.

In 2011, the American Academy of Pediatrics (AAP) endorsed guidelines by the NHLBI on CV health and risk reduction in children and adolescents that outlines age appropriate lipid screening in the pediatric population.[47] NHLBI recommends a fasting lipid profile in children aged 1 to 4 years, only if the child is familial hypercholesterolemia (FH) positive, the child has a parent with dyslipidemia, or if the child has any other risk factors or high-risk conditions. All children should be screened for high cholesterol at least once between the ages of 9 and 11 years, and again between ages 17 and 21 years. It is anticipated that a universal screening will more accurately identify children who are at high risk for CV disease. The guideline also identifies age-specific strategies to reduce risk factors and manage CV disease in children and adolescents. Most children with high cholesterol should be treated with lifestyle modifications including diet and physical activity. Less than 1% of children, primarily those with genetic dyslipidemias, may qualify for cholesterol-lowering medications. In addition to lifestyle interventions, the use of lipid-lowering medications is recommended in general in ages 10 years and older if LDL-C is: ≥ 190 mg/dL, ≥ 160 mg/dL with family history of early heart disease or 1 high- or 2 moderate-level additional risk factors, or > 100 mg/dL if diabetes mellitus is present. The initial LDL-C goal is less than 160 mg/dL, but LDL-C as low as 130 or even 110 mg/dL is warranted if strong CVD family history is present. Drug therapy may be considered for children ages 8 and 9 years with LDL-C persistently greater than 190 mg/dL combined with a strong family history of early CVD or additional risk factors.

In 2015, the FDA approved alirocumab (Praluent) and evolocumab (Repatha), a new class of lipotropic agents. Both are human monoclonal antibodies that bind to proprotein convertase subtilisin/kexin type 9 (PCSK9). Current guidelines have not addressed the role of these agents in non-FH patients. Data obtained during clinical trials have demonstrated that statin efficacy does not increase proportionally with dose.[48,49] This is referred to as the rule of 6%; doubling a statin dose results in approximately an additional 6% decrease in LDL-C, although the actual percentage may vary slightly among individuals. Thus, if it is known that a patient is unlikely to meet a goal LDL-C based on this limitation of statins, the addition of a PCSK9 inhibitor may be appropriate in select patients. Clinical outcomes have not been shown with PCSK9 inhibitors but trials are underway.

PHARMACOLOGY[50,51,52,53,54,55,56,57]

Several non-statin classes of lipotropics are considered in this review.

Apolipoprotein B (apoB) Synthesis Inhibitors

Apolipoprotein B (apo-B) is a structural protein of very low-density lipoproteins (VLDL) and low-density lipoproteins (LDL).[58] Microsomal triglyceride transfer protein (MTP) transfers triglycerides onto apoB during the production of VLDL, a precursor to LDL.[59]

Lomitapide (Juxtapid) directly binds and inhibits MTP, preventing the synthesis of apo-B-containing proteins in enterocytes and hepatocytes. This results in decreased synthesis of VLDL and, thereby, reduced plasma LDL-C levels. MTP inhibitors are not liver-specific and thus block the secretion of both intestinal and hepatic lipoproteins. This lack of inhibition specificity can lead to fat malabsorption in some patients.

Mipomersen (Kynamro) is an antisense oligonucleotide, complementary to the coding region of the human messenger ribonucleic acid (mRNA) for apo B-100, the principal apolipoprotein of LDL. Mipomersen binds to mRNA, forming a hybridization of mipomersen to the cognate mRNA that results in RNase H-mediated degradation of the cognate mRNA thus inhibiting translation of the apo B-100 protein.

Bile Acid Sequestrants

During normal digestion, bile acids are secreted into the intestines. Bile acids emulsify the dietary fat thus facilitating absorption. A major portion of the bile acids is absorbed from the intestinal tract and returned to the liver via the enterohepatic circulation. The bile acid sequestrants, cholestyramine, colestipol (Colestid), and colesevelam (WelChol), bind bile acids in the intestine to form an insoluble complex which is excreted in the feces, thereby interrupting enterohepatic circulation. As the bile acid pool becomes depleted, the hepatic enzyme cholesterol, 7 α-hydroxylase, is upregulated. Upregulation of 7 α-hydroxylase increases the conversion of cholesterol to bile acids with a resulting increase in demand for cholesterol in the liver cells. The hepatic demand for cholesterol causes a dual effect of 1) increasing transcription and activity of the cholesterol biosynthetic enzyme, HMG-CoA reductase and 2) increasing the number of hepatic LDL-C receptors. These compensatory mechanisms increase clearance of LDL-C from the blood, resulting in decreased serum LDL-C levels. In patients with partial biliary obstruction, the reduction of serum bile acid levels reduces excess bile acids deposited in the dermal tissue with resultant decrease in pruritus.

Bile acid sequestrants can reduce LDL-C levels by 12% to 30% and may have a small effect on HDL-C. Reports of impact on TG vary from 0% to 25% reduction. The complementary mechanisms of action of bile acid sequestrants and statins makes them well suited for combination therapy. Combinations of bile acid sequestrants with non-statin lipotropics may be useful in patients who are intolerant to statin therapy.[60] Cholestyramine has been shown to reduce the number of CV events, but colestipol or colesevelam do not have CV clinical outcomes data.

The mechanism of action of colesevelam in glycemic control is unknown.

Cholesterol Absorption Inhibitors

Ezetimibe (Zetia) inhibits cholesterol absorption along the brush border of the small intestine. This leads to a decrease in the delivery of intestinal cholesterol to the liver, reduction of hepatic cholesterol stores, and an increase in cholesterol clearance from the blood. The molecular target of ezetimibe has been shown to be the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols. Ezetimibe inhibits absorption of both dietary cholesterol and cholesterol in bile. Ultimately, ezetimibe reduces total cholesterol (total-C), LDL-C, TG, and apo B, and increases HDL-C in patients with hypercholesterolemia. When ezetimibe is administered with a statin, further improvements on the lipid profile occur.

Addition of ezetimibe to stable bile acid sequestrant therapy has been shown to reduce total-C by 18%, TG by 14%, and LDL-C by 19% after 3 to 4 months. The combination had no effect on HDL-C and was well tolerated.[61]

Fibric Acids

The effects of the fibric acids, fenofibrate (Antara, Fenoglide, Lipofen, Lofibra, Tricor, Triglide), fenofibric acid (Fibricor, Trilipix; the active metabolite of fenofibrate), and gemfibrozil (Lopid), have been explained by the activation of peroxisome proliferator activated receptor alpha (PPARα). Through this mechanism, the fibric acids increase lipolysis and elimination of TG-rich particles from plasma by activating lipoprotein lipase. Fibric acids reduce production of apoproteins C-III, an inhibitor of lipoprotein lipase activity. The resulting fall in TG produces an alteration in the size and composition of LDL-C from small, dense particles, which are thought to be atherogenic due to their susceptibility to oxidation, to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPARα also induces an increase in the synthesis of apoproteins A-I and A-II, as well as HDL-C. Fenofibrate also reduces serum uric acid levels by increasing urinary excretion of uric acid. Each fenofibric acid (Trilipix) delayed-release capsule contains the choline salt of fenofibric acid, which is converted to fenofibric acid in the gastrointestinal tract.[62] Fenofibric acid is thought to be more readily absorbed and less affected by food than fenofibrate.

Gemfibrozil has been shown to reduce the risk of CHD in patients with high TG and low HDL-C.[63,64,65,66] This effect is most significant in patients with diabetes or metabolic syndrome.[67] ACC/AHA advises that gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis. Gemfibrozil use with simvastatin is contraindicated. Fenofibrate, however, does not interfere with statin metabolism and may be less likely to increase the risk for myopathy in patients treated with moderate doses of statins.[68,69]

Fenofibrate did not demonstrate in patients with type 2 diabetes a statistically significant reduction in the risk of first nonfatal MI and CHD death in the FIELD study; although nonfatal MI was significantly reduced.[70,71] In the lipid arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, the combination of fenofibrate and simvastatin did not significantly reduce the rate of fatal CV events, nonfatal MI, or nonfatal stroke, compared with simvastatin monotherapy (HR 0.92, 95% CI 0.79 to 1.08; p=0.32), suggesting against the routine use of combination therapy with fenofibrate and simvastatin to reduce CV risk in the majority of high-risk patients with type 2 diabetes.[72] Based on results from the ACCORD Lipid trial and other clinical trials, in November 2011, the FDA informed the public that fenofibric acid (Trilipix) may not lower a patient's risk of having a MI or stroke and required the manufacturer of Trilipix to conduct a clinical trial to evaluate the CV effects of Trilipix in patients at high risk for CV disease who were already taking statins.[73] In addition, a subgroup analysis of ACCORD showed there was an increase in the risk for major adverse cardiac events in women, relative to men, receiving the combination therapy versus simvastatin alone.[74] The clinical significance of this subgroup finding is unclear, as this finding was not observed in a separate large randomized controlled clinical trial of fenofibrate versus placebo. Data to support the routine use of non-statin drugs in combination with statin therapy to reduce further ASCVD events are lacking; however, non-statin therapy may be considered as adjunct to statin therapy when maximum intensity statin therapy does not lower LDL–C sufficiently to reduce ASCVD event risk in individuals with primary severe elevations of LDL–C.[75] In April 2015, the FDA removed the indication for fenofibric acid (Trilipix) as an adjunct to diet in combination

with a statin to reduce triglycerides and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal.

Niacin (nicotinic acid)

Niacin (nicotinic acid) inhibits lipolysis in adipocytes and possibly inhibits hepatic TG production resulting in a reduction in the synthesis of VLDL that is available for conversion to LDL-C. It may involve several actions, including partial inhibition of the release of free fatty acids from adipose tissue and increased lipoprotein lipase activity. Niacin also increases HDL-C by reducing the hepatic uptake of HDL-C. Nicotinic acid increases HDL-C levels by 15% to 35% and has shown to decrease total cholesterol by 10% and triglycerides by 27%.[76,77] Immediate-release niacin (Niacor) is available with a prescription. It is also available without a prescription. Due to intolerance, patients often need to take aspirin prior to each dose to reduce the vasodilation and flushing associated with niacin immediate-release. To increase tolerance, a film-coated, niacin extended-release (Niaspan) has been developed and is available with a prescription.

Combination therapy with niacin and statins yields a significant reduction in LDL-C and increase in HDL-C.[78] Niacin has been shown to reduce the risk of CHD as monotherapy and in combination with statins.[79,80,81] It also leads to regression of carotid atherosclerosis when given with statins in a small study.[82,83] Niacin caused regression of coronary lesions and reduced CV events in another small study when given in combination with cholestyramine and gemfibrozil.[84]

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) included 3,414 patients with established CVD and atherogenic dyslipidemia. All patients received simvastatin, with or without ezetimibe, at a dose sufficient to maintain LDL-C at 40-80 mg/dL. Patients were randomized to niacin extended-release (ER) or matching placebo.[85] Although niacin ER was effective at raising HDL-C and lowering triglycerides, the trial was halted early due to the lack of incremental benefit on CV risk reduction (including MI and stroke) in the niacin ER plus simvastatin arm versus simvastatin alone (p=0.8).[86,87] In addition, a small, unexplained, increase in the rate of ischemic stroke was observed in the simvastatin plus niacin ER arm compared to simvastatin alone (29 patients versus 18 patients, respectively; p=0.11). Nine of the ischemic strokes in the simvastatin plus niacin ER group occurred in participants who had stopped taking niacin for at least 2 months and up to 4 years before their stroke. Therefore, it is unclear whether niacin contributed to this imbalance in ischemic stroke. The authors note many study limitations, such as that the findings may not be generalizable to all patients with coronary disease or all patients with low HDL-C levels. It remains unclear whether other populations may benefit from such treatment; it is unclear if in the 94% of patients who were taking statins at study entry whether or not they had more stable plaques at baseline which were less likely to rupture, and therefore, had a lower risk of subsequent CV events. The low percentage of women enrolled (15%), the low rate of ethnic minorities (8%), and the 36-month follow-up period may not have been adequate to show a clinical treatment effect of niacin. The AIM-HIGH trial was funded by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institute of Health (NIH) with additional support from Abbott Laboratories. The FDA plans to conduct a review of AIM-HIGH.[88] In April 2015, the FDA removed the indication for niacin ER (Niaspan) in combination with simvastatin or lovastatin for the treatment of primary hyperlipidemia and mixed dyslipidemia when treatment with Niaspan, simvastatin, or lovastatin monotherapy is considered inadequate.

Omega-3 Fatty Acids

Omega-3-acid ethyl esters (Lovaza) is a combination of ethyl esters – 465 mg of eicosapentaenoic acid (EPA) and 375 mg of docosahexaenoic acid (DHA). These 2 fatty acids are found in fish oil and have been shown to be a contributing factor in the beneficial effects of frequent consumption of oily fish.[89] The mechanism of action of omega-3-acid ethyl esters is not completely understood. It is thought that the omega-3-acid ethyl esters may reduce the synthesis of TG by the liver. Beneficial effects on lipids by omega-3-acid ethyl esters include reduced TG and VLDL and increases in HDL-C. Elevations in LDL-C and non-HDL-C may also be observed. In trials done with omega-3-acid ethyl esters, the median percent change in LDL-C was an increase of 49.3% relative to placebo. EPA and DHA have also been shown to demonstrate anti-inflammatory and cardioprotective effects, including possible antiarrhythmic effects and changes in heart rate variability. Omega-3-acid ethyl esters 4 grams per day have been shown to reduce TG by up to 45% in adults with baseline TG ≥ 500 mg/dL.

Icosapent ethyl (Vascepa) is an ethyl ester of EPA only. Icosapent ethyl 4 grams per day has been shown to reduce TG by up to 33.1% in adults with baseline TG ≥ 500 mg/dL while elevations of LDL-C have not been observed.[90]

The use of EPA alone does not affect LDL-C like the combination of EPA and DHA can, due to an increased conversion of VLDL to LDL. In the pivotal clinical trials, treatment with icosapent ethyl was not associated with elevations in LDL-C compared to placebo. The median reduction in triglycerides in omega-3-acid ethyl esters-treated patients from pivotal trials was 27% (33% relative to placebo).

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

Alirocumab (Praluent) and evolocumab (Repatha) are human monoclonal antibodies that bind to PCSK9. PCSK9 binds to low density lipoprotein receptors (LDLR) at the surface of hepatocytes and, thereby, targets internalized LDLR for lysosomal degradation. By inhibiting the binding of PCSK9 to LDLR, these agents increase the number of LDLR available to clear LDL particles, thereby lowering LDL-C.

Significant reductions in LDL-C by approximately 40% to 60% ($p<0.0001$) have been reported for alirocumab compared with placebo. Similar reductions in non-HDL-C levels and apoB were also observed. In phase 3 clinical trials, patients treated with evolocumab experienced an average LDL-C reduction of approximately 30% to 70% ($p<0.0001$).

PHARMACOKINETICS[91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111]

Drug	Bioavailability (%)	Half-Life (hr)	Metabolites	Excretion (%)
Apolipoprotein B Synthesis Inhibitors				
lomitapide (Juxtapid)	7	39.7	major: M1 and M3 (CYP 3A4)	urine: 59.5 feces: 33.4
mipomersen (Kynamro)	54 to 78	1 to 2 months	oligonucleotide metabolites	urine
Bile Acid Sequestrants				
cholestyramine	not absorbed	--	--	feces
colesevelam (Welchol)	not absorbed	--		
colestipol (Colestid)	not absorbed	--		
Cholesterol Absorption Inhibitors				
ezetimibe (Zetia)	35-60	22	ezetimibe glucuronide	urine: 11 feces: 78
Fibric Acids				
fenofibrate (Antara, Fenoglide, Lipofen, Lofibra, Tricor, Triglide)[112]	unknown	16-23	fenofibric acid (active component); glucuronide conjugate	urine: 60 feces: 25
fenofibric acid (Fibricor)	unknown	20	glucuronide conjugate	urine
fenofibric acid (Trilipix)	81	20		
gemfibrozil (Lopid)	100	1.5	3 metabolites	urine: 70 feces: 6
Niacin				
niacin ER (Niaspan)	60-76	--	many metabolites	predominantly urine
niacin IR (Niacor)	88	0.3-0.75	nicotinuric acid	urine
Omega-3 Fatty Acids				
icosapent ethyl (Vascepa)	--	89	acetyl Coenzyme A	hepatic
omega-3-acid ethyl esters (Lovaza)	unknown	--	--	--
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors				
alirocumab (Praluent)	85	17-20 days	--	saturable binding to target (PCSK9) at low concentrations; non-saturable proteolytic pathway at higher concentrations
evolocumab (Repatha)	72	11-17 days	--	

Fenofibrate micronized 67 mg capsule (Lofibra, generic) has been shown to provide similar therapeutic effects to fenofibrate "non-micronized" 100 mg capsule.[113] All currently available fenofibrate products at the highest available dose produce similar plasma concentrations as the fenofibrate 200 mg capsules in single dose studies. Lipofen 150 mg capsules have been shown to be equivalent to Tricor 160 mg tablets under low-fat and high-fat fed conditions. Fenoglide 120 mg tablets have been shown to be equivalent to fenofibrate 130 mg capsules under high-fat conditions. Trilipix 135 mg capsules are equivalent to micronized fenofibrate 200 mg capsules administered under fed conditions. Fibricor 105 mg tablets are equivalent to fenofibrate tablets (TriCor) 145 mg under fasted conditions.

CONTRAINDICATIONS/WARNINGS[114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135]

Apolipoprotein B (apoB) Synthesis Inhibitors

Lomitapide (Juxtapid) and mipomersen (Kynamro) are contraindicated in patients with moderate or severe hepatic impairment (Child Pugh category B or C), or active liver disease, including unexplained persistent elevations of serum transaminases. Both agents carry a black boxed warning due to the risk of hepatotoxicity resulting from increases in transaminases and hepatic steatosis. Both agents can increase hepatic fat, with or without concomitant increases in transaminases. Hepatic steatosis resulting from mipomersen use may be a risk factor for progressive liver disease, including steatohepatitis and cirrhosis. Transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), alkaline phosphatase, and total bilirubin should be measured prior to initiating therapy. During the first year, measurement of ALT and AST should occur monthly and every 3 months thereafter.

Lomitapide is contraindicated in patients who are pregnant. Concomitant use of lomitapide with strong or moderate CYP3A4 inhibitors is also contraindicated.

Caution should be used when lomitapide and mipomersen are taken with other medications that are known to be hepatotoxic (e.g., isotretinoin, amiodarone, high doses of acetaminophen [greater than 4 g/day for 3 days or greater], methotrexate, tetracyclines, and tamoxifen). Due to the fact that alcohol may also increase levels of hepatic fat, patients should not consume more than 1 alcoholic beverage each day.

Due to lomitapide's mechanism of action in the small intestine, the absorption of fat-soluble nutrients may be reduced. Patients taking lomitapide should receive daily supplements containing 400 IU vitamin E, 200 mg linoleic acid, 210 mg alpha-linolenic aid (ALA), 110 mg eicosapentaenoic acid (EPA), and 80 mg docosahexaenoic acid (DHA). Patients with chronic bowel or pancreatic disease may be at increased risk for deficiencies in these nutrients.

The use of mipomersen as an adjunct to LDL apheresis is not recommended.

Bile Acid Sequestrants

Bile acid sequestrants, cholestyramine, colestipol (Colestid), and colesevelam (Welchol), are contraindicated in patients with dysbetalipoproteinemia and/or TG > 400 mg/dL.[136] Colesevelam is contraindicated in patients with bowel obstruction and in patients with hypertriglyceridemia-induced pancreatitis. Cholestyramine is contraindicated in complete biliary obstruction.

Because of its constipating effects, colesevelam is not recommended in patients with gastroparesis, other gastrointestinal motility disorders, and in those who have had major gastrointestinal tract surgery and who may be at risk for bowel obstruction.

Phenylketonuric patients should be aware that colesevelam oral suspension contains 13.5 mg phenylalanine per 1.875 gram packet and 27 mg phenylalanine per 3.75 gram packet.

Cholesterol Absorption Inhibitors

The combination of ezetimibe (Zetia) and a statin is contraindicated in patients with acute liver disease or unexplained persistent elevations in serum transaminases.

Fibric acids

Fenofibrate products (Antara, Fenoglide, Lofibra, Lipofen, Tricor, Triglide) and fenofibric acid (Fibricor, Trilipix) are contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis or persistent liver enzyme elevations or pre-existing gallbladder disease. Gemfibrozil (Lopid) is contraindicated in severe renal or hepatic impairment, including primary biliary cirrhosis, and combination therapy with repaglinide. Caution should be used when prescribing a statin and gemfibrozil together due to an increased risk of myositis and rhabdomyolysis. Concomitant gemfibrozil and simvastatin use is contraindicated.

The use of fibric acids is not recommended in nursing mothers, and it is considered a contraindication for use of Fibricor, Trilipix, and Fenoglide. Fenofibrates and fenofibric acid may cause venothromboembolic disease. Regular periodic monitoring of liver function should be performed for the duration of fenofibrate therapy, and therapy discontinued if enzyme levels persist above 3 times the upper limit of normal (3 x ULN).

Fenofibrates and gemfibrozil can lead to cholelithiasis; therefore, these therapies should be discontinued if gallstones are found.

Reports of dramatic decreases in HDL-C levels (2 mg/dL) have occurred post-marketing in patients on fenofibrate therapy. This can occur weeks to months after initiation of fenofibrate therapy. HDL-C levels return to normal once fibrate therapy is discontinued. Clinical significance is unknown, but it is recommended that HDL-C levels be monitored within the first few months of start of fibrate therapy.

Niacin (nicotinic acid)

Niacin ER (Niaspan) is contraindicated in patients with chronic liver disease, active peptic ulcer disease, or arterial bleeding. Caution should also be used when niacin ER is used in patients with unstable angina or in the acute phase of a myocardial infarction (MI), particularly when such patients are also receiving vasoactive drugs, such as nitrates, calcium channel blockers, or adrenergic blocking agents. Caution should be used with niacin in patients predisposed to gout. Monitor liver function tests in all patients during therapy at approximately 6-month intervals or when clinically indicated. If transaminase levels are above 3 x ULN, or clinical symptoms of hepatic dysfunction are present, niacin should be discontinued. Niacin treatment can increase fasting serum glucose levels. Frequent monitoring of blood glucose should be performed.

Due to an increased risk for myopathy in Chinese patients taking simvastatin 40 mg co-administered with lipid-modifying doses (≥ 1 g/day niacin) of niacin, caution should be used when taking niacin ER/simvastatin (Simcor) in doses that exceed 1 g/20 mg daily to Chinese patients.[137] The cause of the

increased risk of myopathy is unknown. It is also unknown whether the risk for myopathy with co-administration of simvastatin with lipid-modifying doses of niacin-containing products observed in Chinese patients applies to other Asian patients.

Omega-3 Fatty Acids

Omega-3-acid ethyl esters (Lovaza) and icosapent ethyl (Vascepa) should be used with caution in patients with a known history of sensitivity or allergy to fish and/or shellfish. In patients with hepatic impairment, monitor liver transaminases periodically during therapy. Lovaza may increase levels of LDL-C; therefore, periodic LDL-C monitoring during therapy is recommended.

A clinical study has reported a potential association between omega-3-acid ethyl esters and increased recurrences of symptomatic atrial fibrillation or flutter in patients with paroxysmal or persistent atrial fibrillation, particularly within 2 to 3 months after initiation of therapy. This occurred in patients that had no substantial structural heart disease, were taking no anti-arrhythmic therapy (rate control permitted), and were in normal sinus rhythm at baseline.

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

Alirocumab (Praluent) and evolocumab (Repatha) are contraindicated in patients with known hypersensitivity to alirocumab or evolocumab, respectively. Hypersensitivity reactions, such as rash and urticaria have been reported for both alirocumab and evolocumab; pruritus, vasculitis, and reactions requiring hospitalization have been reported with alirocumab. Discontinue if signs or symptoms of an allergic reaction occur.

Risk Evaluation and Mitigation Strategy (REMS)

Due to the risk of hepatotoxicity, lomitapide (Juxtapid) and mipomersen (Kynamro) are only available through a restricted program under the REMS.[138] The goal of the REMS is to educate prescribers regarding the risk of hepatotoxicity, the need to monitor patients during therapy, and to restrict access to therapy with these agents to patients with a clinical or laboratory diagnosis consistent with HoFH. Only certified providers and pharmacies may prescribe and dispense lomitapide and mipomersen. Providers must complete a REMS program prescriber enrollment form, complete a prescriber training module, and submit a REMS prescription authorization form for each new prescription.

DRUG INTERACTIONS[139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160]

Drug	Bile Acid Sequestrants	Cholesterol Absorption Inhibitor	Fibric Acids	Niacin	Omega-3 Fatty Acids	Statins
Apolipoprotein B Synthesis Inhibitors						
lomitapide (Juxtapid)	administration with bile acid sequestrants can reduce lomitapide absorption	slight increase in ezetimibe exposure	decrease in fenofibrate, micronized exposure	increase in nicotinic acid exposure	--	increased risk of myopathy
mipomersen (Kynamro)	--	--	--	--	--	--
Bile Acid Sequestrants						
cholestyramine, colestipol (Colestid)	--	reduced bioavailability of ezetimibe	reduced bioavailability of fenofibrate or fenofibric acid	reduced absorption of niacin	--	--
colesevelam (WelChol)	--	reduced bioavailability of ezetimibe	reduced bioavailability of fenofibrate or fenofibric acid	--	--	--
Cholesterol Absorption Inhibitors						
ezetimibe (Zetia)	reduced bioavailability of ezetimibe	--	increased ezetimibe concentration with risk of cholelithiasis	--	--	--
Fibric Acids						
fenofibrate (Antara, Fenoglide, Lipofen, Lofibra, Tricor, Triglide)	reduced bioavailability of fenofibrate	increased ezetimibe concentration with risk of cholelithiasis	--	--	--	increased risk of myopathy and rhabdomyolysis
fenofibric acid (Fibricor)	reduced bioavailability of fenofibric acid	increased ezetimibe concentration	--	--	--	increased risk of myopathy and rhabdomyolysis
fenofibric acid (Trilipix)	reduced bioavailability of fenofibric acid	increased ezetimibe concentration	--	--	--	increased risk of myopathy and rhabdomyolysis
gemfibrozil (Lopid)	reduced bioavailability of gemfibrozil when given at exact same time as colestipol	increased ezetimibe concentration with risk of cholelithiasis	--	--	--	increased risk of myopathy and rhabdomyolysis

Drug Interactions (continued)

Drug	Bile Acid Sequestrants	Cholesterol Absorption Inhibitor	Fibric Acids	Niacin	Omega-3 Fatty Acids	Statins
Niacin						
niacin ER (Niaspan)	administration with cholestyramine or colestipol reduces absorption of niacin	--	--	--	--	increased risk of myopathy
niacin IR (Niacor)	--	--	--	--	--	increased risk of myopathy
Omega-3 Fatty Acids						
icosapent ethyl (Vascepa)	--	--	--	--	--	--
omega-3-acid ethyl esters (Lovaza)	--	--	--	--	--	--
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors						
alirocumab (Praluent)	--	--	--	--	--	--
evolocumab (Repatha)	--	--	--	--	--	--

Other Drugs

Apolipoprotein B Synthesis Inhibitors

lomitapide (Juxtapid)

CYP3A4 inhibitors – Concomitant use of strong CYP3A4 inhibitors (boceprevir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, tipranavir/ritonavir), and moderate CYP3A4 inhibitors (ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, verapamil) with lomitapide can significantly increase lomitapide exposure and are contraindicated. Lomitapide dose should not exceed 30 mg daily when used with weak CYP3A4 inhibitors (alprazolam, amiodarone, amlodipine, atorvastatin, cimetidine, cyclosporine, fluoxetine, ginkgo, oral contraceptives, ranitidine, ticagrelor). In women taking oral contraceptives, if vomiting or diarrhea occurs while on lomitapide, hormone absorption may be reduced, and use of additional contraceptive methods is warranted.

Warfarin – Lomitapide increases plasma concentrations of warfarin. Monitor the international normalized ratio (INR) appropriately, particularly after lomitapide dosage change.

Simvastatin and lovastatin – Lomitapide increases simvastatin exposure. Reduce simvastatin dose by 50% when initiating lomitapide. Simvastatin dose should not exceed 20 mg daily or 40 mg daily for patients who have been tolerant to simvastatin 80 mg daily for at least 1 year. Although not studied, since metabolizing enzymes are similar for lovastatin and simvastatin, lovastatin dose reduction should be considered with concomitant use of lomitapide.

P-glycoprotein Substrates (P-gp) – Co-administration of lomitapide with P-gp substrates (e.g., aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, fexofenadine, saxagliptin, sitagliptin) may

increase the absorption of the P-gp substrate. Dose reduction of the P-gp substrate should be considered when used concomitantly with lomitapide.

mipomersen (Kynamro)

Mipomersen is not metabolized by CYP450 enzymes. No clinically-relevant pharmacokinetic interactions were reported between mipomersen and simvastatin, ezetimibe, or warfarin.

Bile Acid Sequestrants – cholestyramine, colestipol (Colestid), and colesevelam (WelChol)

Diltiazem, mycophenolate – The bile acid sequestrants reduce the absorption of diltiazem and mycophenolate, regardless of the time of administration of the interacting drugs relative to each other.[161,162] Concomitant use of mycophenolate with the bile acid sequestrants is not recommended.

Warfarin – Cholestyramine can reduce serum levels of warfarin by interfering with its enterohepatic circulation; dosage adjustments may be necessary.[163]

Vitamins – Bile acid sequestrants may decrease the absorption of fat-soluble vitamins A, D, E, and K. Patients on oral vitamin supplementation should take their vitamins at least 4 hours prior to a bile acid sequestrant. Caution should be exercised when treating patients with a susceptibility to deficiencies of vitamin K (e.g., patients on warfarin, patients with malabsorption syndromes) or other fat-soluble vitamins. Chronic use of cholestyramine can result in a folate deficiency. Supplementation may be necessary.

Colesevelam reduces levels of cyclosporine, glimepiride, glipizide, glyburide, levothyroxine, olmesartan, and oral contraceptives containing ethinyl estradiol and norethindrone. These agents should be administered at least 4 hours prior to colesevelam. Colesevelam increases the exposure of extended-release metformin. Colesevelam may also interact with concomitant therapy with phenytoin, warfarin, or other narrow therapeutic index drugs. Colesevelam can increase triglycerides in combination with insulin or sulfonylureas.

Since cholestyramine and colestipol may bind other drugs given concurrently, it is recommended that patients take other drugs at least 1 hour before or 4 to 6 hours after cholestyramine (or as great an interval as possible) to avoid impeding their absorption.

Cholesterol Absorption Inhibitor – ezetimibe (Zetia)

Cyclosporine – Using cyclosporine and ezetimibe together may result in increased plasma levels of both drugs; the mechanism of this interaction is unknown.

Fibric Acids – fenofibrate (Antara, Fenoglide, Lipofen, Tricor, Triglide), fenofibric acid (Fibricor, Trilipix), and gemfibrozil

Warfarin – Concomitant administration of fibric acids and warfarin increases the INR and the risk of bleeding.

Cyclosporine – Concomitant use of cyclosporine and fenofibrate or fenofibric acid (Fibricor, Trilipix) may decrease renal function.

Oral hypoglycemics – The concurrent use of gemfibrozil with glyburide (Diabeta®, Glynase®), pioglitazone (Actos®) or rosiglitazone (Avandia®) may result in enhanced hypoglycemic effect.[164,165,166,167] The use of gemfibrozil with repaglinide (Prandin®) is contraindicated due to a significant increase in serum concentrations of the oral hypoglycemic.[168]

Colchicine – Myopathy, including rhabdomyolysis, has been reported with concurrent use of fenofibrate or gemfibrozil with colchicine. Use caution when prescribing both agents.

Statins – The concomitant administration of gemfibrozil with simvastatin is contraindicated.

Niacin – niacin IR and ER (Niacor and Niaspan)

Warfarin – Caution should be observed when niacin is administered concomitantly with anticoagulants. Niacin has been associated with small but statistically significant increases (mean 4%) in prothrombin time (PT). Monitor INR periodically.

Lovastatin and simvastatin – Combination therapy with Niaspan and lovastatin or simvastatin should not exceed doses of 2,000 mg Niaspan and 40 mg lovastatin or simvastatin daily.

Omega-3-Fatty Acids – omega-3-acid-ethyl esters (Lovaza), icosapent ethyl (Vascepa)

Anticoagulants - Omega-3-acids may prolong bleeding time. Patients taking Lovaza or Vascepa and an anticoagulant or other drug affecting coagulation should be monitored periodically.

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors – alirocumab (Praluent), evolocumab (Repatha)

No relevant drug-drug interactions for alirocumab or evolocumab are listed in the prescribing information.

ADVERSE EFFECTS[169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189]

Drug	Abd. Pain	Back pain	Headache	Abnormal LFTs	Constipation	Dyspepsia
Apolipoprotein B Synthesis Inhibitors						
lomitapide (Juxtapid)	34	14	10	21	21	38
mipomersen (Kynamro)	3 (1)	nr	12 (9)	12 (1)	nr	nr
Bile Acid Sequestrants						
cholestyramine	reported	nr	nr	nr	common	reported
colesevelam (Welchol)	5 (5)	3 (6)	3.9 (3.1)	nr	11 (7)	8 (3)
colestipol (Colestid)	reported	reported	reported	reported	common	reported
Cholesterol Absorption Inhibitors						
ezetimibe (Zetia)	3 (2.8)	4 (4)	nr	nr	nr	nr
Fibric Acids						
fenofibrate (Antara, Fenoglide, Lofibra, Lipofen, Tricor, Triglide)	4.6 (4.4)	3.4 (2.5)	3.2 (2.7)	2-8 (1.4)	2.1 (1.4)	reported
fenofibric acid (Fibricor)	4.6 (4.4)	3.4 (2.5)	3.2 (2.7)	7.5 (1.4)	2.1 (1.4)	3.7
fenofibric acid (Trilipix)	4.6 (4.4)	3.4 (2.5)	3.2 (2.7)	7.5 (1.4)	2.1 (1.4)	3.7
gemfibrozil (Lopid)	9.8 (5.6)	nr	1.2 (1.1)	1	1.4 (1.3)	19.6 (11.9)
Niacin						
niacin ER (Niaspan)	2-5 (3)	nr	8-11 (15)	reported	nr	2-5 (8)
niacin IR (Niacor)	nr	nr	reported	reported	nr	reported
Omega-3 Fatty Acids						
icosapent ethyl (Vascepa)	nr	nr	nr	nr	nr	nr
omega-3-acid ethyl esters (Lovaza)	nr	nr	nr	reported	reported	3.1 (2.6)
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors						
alirocumab (Praluent)	nr	nr	nr	2.5 (1.8)	nr	nr
evolocumab (Repatha)	nr	2.3 (2.2)	4 (3.6)	nr	nr	nr

nr= not reported LFTs = liver function tests

Adverse effects are indicated as percentage occurrence. Adverse effects data are compiled from package inserts and cannot be considered comparative or all inclusive. Incidences for the placebo group are indicated in parentheses.

Apolipoprotein B synthesis inhibitors: Other commonly reported adverse reactions for lomitapide were gastrointestinal in nature, reported by 93% of patients on lomitapide in clinical trials. Other adverse effects reported include influenza (21%), decreased weight (24%), chest pain (24%), fatigue (17%), and pharyngolaryngeal pain (14%).

Other commonly reported adverse reactions reported for mipomersen were injection site reactions (84%), flu-like symptoms (30%), and nausea (14%).

Bile acid sequestrants: Less flatulence, constipation, dyspepsia, and other gastrointestinal effects have been reported with colesevelam than with cholestyramine and colestipol. However, no direct comparisons are available.[190] Colesevelam can increase triglycerides in combination with insulin or sulfonylureas. In the diabetes trials, the overall incidence of hypoglycemia was 3% in patients on colesevelam versus 2.3% in placebo-treated patients.

Cholesterol Absorption Inhibitor: Cases of myopathy and rhabdomyolysis have been reported in patients treated with ezetimibe co-administered with a statin and with ezetimibe administered alone. Risk for skeletal muscle toxicity increases with higher doses of statin, advanced age (greater than 65 years), hypothyroidism, renal impairment, and depending on the statin used, concomitant use of other drugs.

A systematic review of 18 randomized controlled trials of combination statin and ezetimibe trials was performed to assess risk in 14,471 patients.[191] Compared with statin monotherapy, combination therapy did not result in significant absolute increases in risks of myalgias (risk difference -0.033; 95% CI, -0.06 to -0.01), creatine kinase increases (risk difference 0.011; 95% CI, -0.02 to 0.04), rhabdomyolysis (risk difference -0.003; 95% CI, -0.01 to 0.004), transaminase increases (risk difference -0.003; 95% CI, -0.01 to 0.005), gastrointestinal adverse events (risk difference 0.005; 95% CI, -0.03 to 0.04), or discontinuations because of an adverse event (risk difference -0.005; 95% CI, -0.03 to 0.02). This systematic review showed that the addition of ezetimibe to statin therapy did not increase the risk of myalgias, creatine kinase levels, rhabdomyolysis, transaminase levels, gastrointestinal adverse events, or discontinuations due to adverse events.

Fibric acids: Fibric acids may cause cholelithiasis. Fenofibrate and fenofibric acid may also cause myositis, myopathy, and rhabdomyolysis; this risk may be further increased when given concomitantly with statins.

Fenofibrate use is associated with reversible elevations in serum creatinine. The clinical significance of this is unknown. Renal function should be monitored in patients with or at risk for renal insufficiency, such as the elderly and patients with diabetes. In a study that assessed renal outcomes in elderly adults within 90 days of a new fibrate prescription, patients who received fibrates (n=19,072) were more likely to be hospitalized for an increase in serum creatinine level (adjusted odds ratio, 2.4 [95% CI, 1.7 to 3.3]) and were more likely to consult a nephrologist (absolute risk difference, 0.15% [CI, 0.01% to 0.29%]; adjusted odds ratio, 1.3 [CI, 1 to 1.6]), than patients who received ezetimibe (n=61,831).[192] There were no differences between groups in the risk for all-cause mortality or receiving dialysis for severe acute kidney injury. In a subpopulation of 1,110 patients (fibrates, n=220; ezetimibe, n=890), 9.1% of fibrate users and 0.3% of ezetimibe users had an increase in serum creatinine level of at least 50%. Risks were greater among fibrate users with chronic kidney disease.

Niacin: Flushing has been reported to occur in up to 88% of patients receiving niacin ER. Hyperglycemia and/or hyperuricemia (and/or gout) have also been associated with the use of niacin.

Omega-3-acids: Arthralgia has been reported with icosapent ethyl use.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors: Common adverse reactions with the PCSK9 inhibitors include nasopharyngitis, injection site reactions, upper respiratory tract infection/inflammation, urinary tract infections, diarrhea, and myalgia.

Similar incidence of neurocognitive events were reported for the PCSK9 inhibitors compared to placebo (0.8% and 0.7% of patients treated with alirocumab and placebo, respectively; 0.2% or less of patients treated with evolocumab or placebo).

A total of 1.2% of patients treated with alirocumab developed neutralizing antibodies (NAb) on at least one occasion as compared with no patients treated with control and 0.3% of patients both tested positive for NAb and exhibited transient or prolonged loss of efficacy. A total of 0.1% of patients treated with evolocumab tested positive for binding antibody development; however, none of these patients who were further tested for NAb tested positive. There was no evidence that the presence of anti-drug binding antibodies impacted the pharmacokinetic profile, clinical response, or safety of evolocumab. The long-term consequences of continuing treatment in the presence of persistent NAb are unknown.

SPECIAL POPULATIONS[193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213]

Pediatrics

Many of the products in the Other Lipotropics category do not have safety and effectiveness data in the pediatric population. Limited data are available regarding use in children for cholestyramine and colestipol.[214] Pediatric patients have been reported to experience hyperchloremic metabolic acidosis or gastrointestinal obstruction with the use of cholestyramine.[215] Colesevelam (Welchol) is approved to reduce LDL-C in boys and postmenarchal girls, aged 10 to 17 years, with heterozygous familial hypercholesterolemia (HeFH) as monotherapy or in combination with a statin. Colesevelam has not been studied in children younger than 10 years. Ezetimibe (Zetia) has been used in a limited number of children ages 10 years and older, but the safety and effectiveness have not been established in patients less than 10 years of age. Niacin has been used safely for the treatment of nutritional deficiencies; however, safety and effectiveness of niacin for the treatment of hyperlipidemias have not been established in pediatrics. Safety and efficacy of fibric acids (fenofibrate, fenofibric acid, and gemfibrozil), lomitapide (Juxtapid), mipomersen (Kynamro), omega-3-acid ethyl esters (Lovaza), and icosapent ethyl (Vascepa) have not been established in pediatrics.

In a multi-center, double-blind, controlled study followed by an open-label phase, 142 boys and 106 postmenarchal girls, 10 to 17 years of age, with HeFH were randomized to receive either ezetimibe co-administered with simvastatin or simvastatin monotherapy. The mean baseline LDL-C value was 225 mg/dL in the combination group compared to 219 mg/dL in the monotherapy group. The patients received combination of ezetimibe and simvastatin (10 mg, 20 mg, or 40 mg) or simvastatin monotherapy (10 mg, 20 mg, or 40 mg) for 6 weeks, co-administered ezetimibe/simvastatin 10/40 mg or simvastatin 40 mg monotherapy for the next 27 weeks, and open-label co-administered ezetimibe and simvastatin (10 mg, 20 mg, or 40 mg) for 20 weeks thereafter. At week 6, the mean percent difference between treatment groups for LDL-C was -15% (95% CI, -18 to -12). Results at week 33 were consistent with those at week 6.

The safety and efficacy of colesevelam in pediatric patients were evaluated in an 8-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter, study followed by an open-label phase, in 194 boys and postmenarchal girls 10 to 17 years of age with HeFH, taking a stable dose of an FDA-approved statin (with LDL-C > 130 mg/dL) (24% of patients) or naïve to lipid-lowering therapy (with LDL-C > 160 mg/dL) (76% of patients).[216] The mean baseline LDL-C was approximately 199 mg/dL. During the double-blind treatment period, patients were assigned randomly to treatment: colesevelam 3.8 g/day (n=64), colesevelam 1.9 g/day (n = 65), or placebo (n = 65). A total of 186 patients completed the double-blind treatment period. After 8 weeks of treatment, colesevelam 3.8 g/day significantly decreased plasma levels of LDL-C (-13%), total cholesterol (-7%), and significantly increased HDL-C (+6%) compared to placebo ($p \leq 0.05$ for all comparisons). There was a non-significant increase in TG (+5%) versus placebo. During the open-label treatment period, patients were treated with colesevelam 3.8 g/day. A total of 173 patients completed 26 weeks of treatment. Results at week 26 were consistent with those at week 8.

The safety and efficacy of alirocumab (Praluent)in pediatric patients have not been established. The safety and efficacy of evolocumab (Repatha) for the treatment of adolescents ages 13 to 17 years old with HoFH who require additional LDL-C lowering was established in a placebo-controlled, 12-week trial (n=10 [n=7, evolocumab; n=33 placebo]). Additional details on this trial, which also included adults, are described in the Clinical Studies section below. The safety and efficacy of evolocumab in pediatric patients with primary hyperlipidemia or HeFH or in patients younger than 13 years old with HoFH have not been established.

Pregnancy

Cholestyramine and colesevelam are non-absorbable and therefore considered Pregnancy Category B. Mipomersen is also Pregnancy Category B. Niacin is Pregnancy Category A for recommended daily allowance nutrient amounts; however, for the treatment of hyperlipidemia, niacin is considered Pregnancy Category C. Lomitapide is Pregnancy Category X, therefore contraindicated during pregnancy. Females of reproductive potential should have a negative pregnancy test before starting lomitapide therapy and should use effective contraception during therapy. Females on lomitapide who become pregnant should stop therapy immediately and notify their healthcare provider. The remaining products in this class are Pregnancy Category C. There are no adequate and well-controlled trials of alirocumab or evolocumab in pregnant women.

Gender

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial was a double-blind, placebo-controlled study that evaluated if fenofibrate reduced major CV events in patients with type 2 diabetes and whether there were gender differences in fenofibrate response.[217] A total of 3,657 women and 6,138 men with type 2 diabetes and not on statin therapy received either fenofibrate 200 mg/day or placebo for 5 years. LDL-C, HDL-C, non-HDL-C, and apolipoproteins (apo) A-1 and B improved in both men and women (all $p<0.001$). A greater reduction was seen in women for all measures, except apo A-1. Fenofibrate reduced total CV outcomes (CV death, fatal and non-fatal stroke, and carotid and coronary revascularization) by 30% in women ($p=0.008$) and 13% in men ($p=0.07$).

Hepatic/Renal Impairment

Fenofibrates (Antara, Fenoglide, Lofibra, Lipofen, Tricor, Triglide) and fenofibric acid (Fibricor, Trilipix) should be dose adjusted in renal impairment, unless severe impairment, when use is contraindicated.

Their use has not been evaluated in hepatic impairment, but is contraindicated in hepatic dysfunction including patients with primary biliary cirrhosis or unexplained persistent liver function abnormalities.

Ezetimibe is not recommended in moderate to severe hepatic impairment.

No dosage adjustment of ezetimibe is necessary with renal impairment. When ezetimibe is given with simvastatin in patients with moderate to severe renal impairment (estimated glomerular filtration [eGFR] < 60 mL/min/1.73 m^2), doses of simvastatin exceeding 20 mg should be used cautiously and with close monitoring for myopathy.

Niacin-containing products should be used with caution in patients with renal impairment, past history of liver disease, and in patients who consume substantial quantities of alcohol. Active liver disease, unexplained transaminase elevations, and significant or unexplained hepatic dysfunction are contraindications to the use of niacin.

Mipomersen is contraindicated in patients with moderate or severe hepatic impairment, or active liver disease, including unexplained persistent elevations of serum transaminases. The safety and efficacy of mipomersen have not been established in patients with known renal impairment or in patients undergoing renal dialysis. It is not recommended in patients with severe renal impairment, clinically significant proteinuria, or on renal dialysis.

Lomitapide is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C). Lomitapide exposure is significantly increased in patients with mild hepatic impairment (Child-Pugh A) or with end-stage renal disease receiving dialysis; therefore, lomitapide dosage should not exceed 40 mg daily. Although not studied, it is possible that lomitapide exposure is increased in those patients with mild, moderate, or severe renal impairment, not on dialysis; therefore, caution should be used.

Monitor liver function (ALT, AST) in patients with hepatic impairment periodically during therapy with omega-3-acid ethyl esters and icosapent ethyl.

No dose adjustment is necessary for patients with mild to moderate hepatic or renal impairment using alirocumab or evolocumab. Neither alirocumab nor evolocumab have been studied in patients with severe hepatic or renal impairment.

DOSAGES[218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238]

Drug	Availability	Dose	Comments
Apolipoprotein B Synthesis Inhibitors			
lomitapide (Juxtapid)	5, 10, 20, 30, 40, 60 mg capsules	Initiate with 5 mg daily; Titrate to 10 mg daily after ≥ 2 weeks, then 4-week intervals to 20 mg, 40 mg, 60 mg; Do not exceed 60 mg per day	Swallow capsules whole Take with water and without food, at least 2 hours after the evening meal
mipomersen (Kynamro)	200 mg/1 mL solution in single-use vial and prefilled syringe	200 mg once weekly as a subcutaneous injection	Do not administer intramuscularly or intravenously Administer dose on the same day each week; if a dose is missed, the dose should be given at least 3 days from the next weekly dose
Bile Acid Sequestrants			
cholestyramine	powder	1 to 2 packets or scoopfuls twice daily	Mix with 2 to 6 ounces of water or pulpy fruit (applesauce)
colesevelam (WelChol)	625 mg tablets 3,750 mg packet powder oral suspension	Hyperlipidemia or Type 2 DM: 3,750 mg daily in 1 or 2 divided doses	May be increased to 4,375 mg daily Take with meals Oral suspension may be mixed with water, fruit juice, or diet soft drinks prior to ingestion
colestipol (Colestid)	1 g tablets	2 g once or twice daily	Increase by 2 g at 1- to 2-month intervals to a maximum of 16 g daily
	5 g/tsp granules	5 to 30 g daily	Increase daily dose by 5 g at 1- to 2-month intervals
Cholesterol Absorption Inhibitors			
ezetimibe (Zetia)	10 mg tablets	10 mg daily	Take with or without food
Fibric Acids			
fenofibrate	67, 134, 200 mg capsules	67-200 mg daily	Must be taken with food
	54, 160 mg tablets	54-160 mg daily	Must be taken with food
fenofibrate (Antara)	30, 43, 90, 130 mg capsules	30-130 mg daily	Take without regard to meals
fenofibrate (Fenoglide)	40, 120 mg tablets	40-120 mg daily	Take with food
fenofibrate (Lipofen)	50, 150 mg capsules	50-150 mg daily	Take with food
fenofibrate (Tricor)	48, 145 mg tablets	48-145 mg daily	Take without regard to meals
fenofibrate (Triglide)	160 mg tablets	50-160 mg daily	Take without regard to meals
fenofibric acid (Fibricor)	35, 105 mg tablets	35-105 mg daily	Take without regard to meals
fenofibric acid (Trilipix)	45, 135 mg delayed release capsules	45-135 mg daily	Take without regard to meals
gemfibrozil (Lopid)	600 mg tablets	600 mg twice daily	Given 30 minutes prior to meal

Dosages (continued)

Drug	Availability	Dose	Comments
Niacin			
niacin ER (Niaspan)	500, 750, 1,000 mg tablets	500-2,000 mg at bedtime	Titrate dose up every 4 weeks May pre-administer aspirin to reduce flushing Take at bedtime after low-fat snack
niacin IR (Niacor)	500 mg tablets	1-2 g twice or 3 times daily	May pre-administer aspirin to reduce flushing Take at bedtime after low-fat snack
Omega-3 Fatty Acids			
icosapent ethyl (Vascepa)	1 g capsules	2 g twice daily	Take with food Swallow capsules whole
omega-3-acid ethyl esters (Lovaza)	1 g capsules	4 g daily in 1 or 2 divided doses	Take with meal(s) Swallow capsules whole
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors			
alirocumab (Praluent)	75 mg/1 mL and 150 mg/1 mL single-use prefilled pen or syringe	75 mg subcutaneously once every 2 weeks; dose may be increased to a maximum of 150 mg administered every 2 weeks	Patients can self-administer the pen or syringe with proper training; Administration should be in the thigh, abdomen, or upper arm. Rotate the injection site with each injection
evolocumab (Repatha)	140 mg/1 mL prefilled autoinjector or syringe	HeFH or with primary hyperlipidemia: 140 mg subcutaneously once every 2 weeks or 420 mg (3 syringes) once monthly; HoFH: 420 mg (3 syringes) once monthly	Patients can self-administer the pen or syringe with proper training; Administration should be in the thigh, abdomen, or upper arm. Rotate the injection site with each injection For the 420 mg dose, administer 3 injections consecutively within 30 minutes

Regular and extended-release formulations of niacin are not interchangeable.

Patients with end-stage renal disease on dialysis or with baseline mild hepatic impairment should not exceed lomitapide 40 mg daily.

There are 3 combination statin products, ezetimibe/simvastatin (Vytorin), niacin ER/simvastatin (Simcor), and niacin ER/lovastatin (Advicor®). They are not discussed in this review.

Antara 43 mg and 130 mg capsules will be discontinued and replaced by Antara 30 mg and 90 mg capsules.

LDL-C levels should be measured within 4 to 8 weeks of initiating or titrating therapy with PCSK9 inhibitors to assess response and adjust the dose, as needed.

For missed doses of alirocumab the patient should administer the injection within 7 days from the missed dose and then resume the original dosing schedule. If the missed dose is not administered within 7 days, then the patient should wait until the next dose on the original schedule. If a dose of evolocumab is missed, the patient should administer the dose as soon as possible if there are more than 7 days until the next scheduled dose, or omit the missed dose and administer the next dose according to the original schedule.

Alirocumab and evolocumab should be refrigerated. Evolocumab may be kept at room temperature in the original carton for up to 30 days; alirocumab should be allowed to warm to room temperature for 30 to 40 minutes prior to use (time out of refrigeration should not exceed 24 hours).

CLINICAL TRIALS

Search Strategies

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled comparative trials for FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship funding must be considered, the studies in this review have also been evaluated for validity and importance.

The effects of the drugs in this class on lipids are well documented. To date, however, clinical outcomes have not been established for colesevelam (Welchol), colestipol (Colestid), fenofibrates, lomitapide (Juxtapid), mipomersen (Kynamro), prescription strength omega-3-acid ethyl esters (Lovaza), or icosapent ethyl (Vascepa).[239, 240,241,242,243,244,245,246,247,248]

cholestyramine

The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), a multicenter, double-blind study, tested the efficacy of cholesterol lowering in reducing risk of CHD.[249,250] A total of 3,806 asymptomatic middle-aged (35 to 59 years) men with primary hypercholesterolemia were randomized to receive cholestyramine 24 g/day or placebo for an average of 7.4 years. Both groups followed a moderate cholesterol-lowering diet. The cholestyramine group experienced average reductions in total-C of 13.4% and in LDL-C of 20.3%. The cholestyramine group experienced a 19% reduction in risk ($p<0.05$) of the primary composite endpoint of definite CHD death and/or definite nonfatal MI; this reflected a 24% reduction in definite CHD death and a 19% reduction in nonfatal MI. The cumulative 7-year incidence of the primary endpoint was 7% in the cholestyramine group and 8.6% in the placebo group. In addition, the incidence rates were reduced for new positive exercise tests (by 25% compared to placebo; $p<0.001$) and new onset angina (by 20%; $p<0.01$). The incidence of coronary bypass surgery was similar in each group. The risk of death from all causes was reduced by 7% (p=NS) in the cholestyramine group; the magnitude of this decrease was less than for CHD endpoints because of a greater number of violent and accidental deaths in the cholestyramine group.

cholestyramine, gemfibrozil, and niacin IR (Niacor)

A randomized, double-blind, placebo-controlled trial assessed the effects of gemfibrozil, niacin immediate-release, and cholestyramine on the composite outcome of MI, transient ischemic attack or stroke, CV death, CV procedures, or hospitalization for angina.[251] A total of 143 military retirees with

low HDL-C (mean 34 mg/dL) and documented CAD were randomized to the combination of therapy or placebos. Active treatment included gemfibrozil 600 mg twice daily, niacin 500 mg titrated to 3,000 mg daily, and cholestyramine 2 gm titrated to 16 gm daily. Aggressive dietary and lifestyle changes were followed for 6 months prior to randomization. Cardiac angiography was performed at baseline and after 30 months of follow-up. The active treatment group experienced a total-C reduction of 20% (95% CI, 14.8 to 24.3%), LDL-C reduction of 26% (95% CI, 19.1 to 33.7%), triglyceride (TG) reduction of 50% (95% CI, 40.5 to 59.2%), and an increase in HDL-C of 36% (95% CI, 28.4 to 43.5%). The composite endpoint was reached by 26.4% of the placebo group compared to 12.7% of the active treatment group, an absolute difference of 13.7% (95% CI, 0.9 to 26.5%). There were no significant differences in the individual clinical event rates between the 2 small groups. On repeat cardiac angiography, the active treatment group was observed to have slight regression, whereas the placebo group experienced progression over the 30 months. Flushing, skin rash, and GI intolerance were more common in the active treatment group, and flushing problems could have lead to the possibility of unblinding.

colesevelam (Welchol) and metformin, sulfonylurea, and insulin

Efficacy of colesevelam in type 2 diabetes mellitus was evaluated in 3 double-blind, placebo-controlled trials in combination with metformin, sulfonylurea, or insulin.[252] A total of 1,018 patients with baseline HbA1c of 7.5 to 9.5% took colesevelam 3.75 g/day as 3 tablets twice daily with meals or as 6 tablets with dinner for 26 weeks. In all 3 trials, HbA1c was reduced by 0.5% compared to placebo ($p<0.001$ for all comparisons). Colesevelam increased TG levels in patients taking concurrent insulin or sulfonylurea but not in the metformin study.

A 26-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study evaluated the effects of colesevelam 3.75 g daily in 316 patients with inadequately controlled type 2 diabetes mellitus (baseline HbA1c of 8.1%), who were receiving metformin monotherapy or metformin combined with additional oral anti-diabetes drugs.[253] Colesevelam lowered the mean HbA1c level by -0.54% compared with placebo at week 26 ($p<0.001$). Similar results were observed in the metformin monotherapy (-0.47%, $p=0.002$) and combination therapy cohorts (-0.62%, $p<0.001$). Colesevelam also significantly reduced fasting plasma glucose (-13.9 mg/dL, $p=0.01$), total-C (-7.2%, $p<0.001$), LDL-C (-15.9%, $p<0.001$), and apo B (-7.9%, $p<0.001$). TG, HDL-C, and apolipoprotein A-I levels were not statistically significantly increased.

colesevelam (Welchol) and insulin

A 16-week, randomized, double-blind, placebo-controlled, parallel group, multicenter study of 287 patients with type 2 diabetes mellitus evaluated the efficacy and safety of colesevelam 3.75 g/day in patients already receiving insulin alone or in combination with oral antidiabetic agents with inadequate glycemic control (mean baseline HbA1c 8.3%).[254] The mean (SE) change in HbA1c was -0.41% (0.07%) versus 0.09% (0.07%) for colesevelam versus placebo, respectively. The treatment difference was 0.5% (SE, 0.09%; 95% CI, -0.68 to -0.32; $p<0.001$). There was a 12.8% reduction in LDL-C levels in the colesevelam group versus placebo ($p<0.001$). Median TG levels increased significantly in the colesevelam group.

colesevelam (Welchol) and ezetimibe (Zetia)

A randomized, double-blind, placebo-controlled, parallel group, multicenter study compared colesevelam 3.8 gm/day plus ezetimibe 10 mg daily to placebo plus ezetimibe 10 mg daily in 86

patients for 6 weeks.[255] The primary endpoint was the mean percentage change in LDL-C reduction and secondary endpoints were mean absolute change in LDL-C, mean absolute and mean percentage change in HDL-C, non-HDL-C, TC, apo A-I, and apo B, and mean absolute change and percentage changes in TG and C-reactive protein (CRP). Colesevelam plus ezetimibe produced a mean percentage change in LDL-C of -32.3% versus -21.4% with ezetimibe monotherapy (p<0.0001). The combination therapy was significantly more effective than ezetimibe alone in reducing total-C, non-HDL-C, and apo-B, and increasing apo A-I (p<0.005 for all). Neither regimen significantly increased TG (p=NS). Both treatment arms were generally well tolerated.

ezetimibe (Zetia) and fenofibrate

A randomized, double-blind, placebo-controlled, parallel-group, multicenter, 12-week study of 625 patients with mixed hyperlipidemia compared fenofibrate 160 mg/day, ezetimibe 10 mg/day, or the combination of fenofibrate 160 mg/day and ezetimibe 10 mg/day.[256] At baseline and at 12 weeks, the Vertical Auto Profile II method was used to measure the cholesterol associated with two very low-density lipoprotein (VLDL) subfractions (VLDL-C1 + 2 and VLDL-C3), intermediate-density lipoproteins (IDL-C), and 4 LDL-C subfractions (LDL-C1 through LDL-C4, from most buoyant to most dense), lipoprotein (Lp) (a), and 2 HDL-C subfractions (HDL-C2 and HDL-C3). The LDL-C particle size was determined using segmented gradient gel electrophoresis. Fenofibrate reduced cholesterol mass within VLDL, IDL, and dense LDL-C (primarily LDL-C4) subfractions, and increased cholesterol mass within the more buoyant LDL-C2 subfraction, consistent with a shift to a more buoyant LDL-C peak particle size. Ezetimibe reduced cholesterol mass within all of the apolipoprotein B-containing particles (e.g., VLDL-C, IDL-C, and LDL-C) but did not lead to a shift in the LDL-C particle size distribution profile. Co-administration of fenofibrate and ezetimibe promoted more pronounced reductions in VLDL-C, IDL-C, and LDL-C, and a preferential decrease in dense LDL-C subfractions. Fenofibrate and combination therapy promoted similar increases in HDL-C2 and HDL-C3.

fenofibrate (Antara, Fenoglide, Lipofen, Tricor, Triglide)

In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, 9,795 patients with type 2 diabetes and no signs of prior CV disease were randomized to fenofibrate 200 mg/day or placebo for a median of 5 years.[257] Patients were 50 to 75 years, had total-C of 116 to 251 mg/dL, and did not take statin therapy prior to study enrollment. In the double-blind trial, the primary outcome of coronary events (CHD death and non-fatal MI) occurred in 5.9% and 5.2% of placebo and fenofibrate groups, respectively, for a relative risk reduction of 11% (p=0.16). The fenofibrate group had a 24% relative risk reduction for non-fatal MI with a nonsignificant increase in CHD mortality. The excess of CHD deaths in the fenofibrate group (110 versus 93 events in the placebo group) was mostly due to an increase in sudden cardiac death (70 versus 64 events, respectively). The secondary endpoint of total CV events (CV mortality, MI, stroke, and coronary and carotid revascularization) occurred in 12.5% of patients in the fenofibrate group and 13.9% of patients in the placebo group (p=0.035). This reduction was primarily related to a 24% relative risk reduction in the incidence of MI (p=0.010) and 21% relative risk reduction in coronary revascularization (p=0.003). There was a significant 11% reduction in the secondary outcomes (HR 0.89, 95% CI 0.8 to 0.99, p=0.04). There was a non-significant 11% (HR 1.11, 95% CI 0.95, 1.29, p=0.41) and 19% (HR 1.19, 0.9 to 1.57, p=0.22) increase in total mortality and CHD mortality, respectively, with fenofibrate compared to placebo. By the end of the study, twice as many patients in the placebo group (32%) were receiving statins than in the fenofibrate group (16%; p<0.0001). After adjusting for statin use, investigators estimated that fenofibrate reduced the risk of

CHD events by 19% (p=0.01) and of total CV disease events by 15% (p=0.004). Fenofibrate was also associated with less progression of albuminuria (p=0.002). Fenofibrate was well tolerated with a discontinuation rate similar to placebo. Nonsignificant increases in pancreatitis and pulmonary embolism were reported in the fenofibrate group.

The SAFARI study was a randomized, double-blind, active-controlled, multicenter, 18-week (6-week diet and placebo run-in period) study of 618 patients with mixed dyslipidemia.[258] Simvastatin 20 mg daily and fenofibrate 160 mg daily was compared to simvastatin monotherapy 20 mg daily to evaluate efficacy and safety. From baseline to week 12, median TG levels decreased 43% in the combination group and 20.1% in the simvastatin monotherapy group (treatment difference -23.6%, p<0.001). Mean LDL-C decreased 31.2% and 25.8% (treatment difference -5.4%, p<0.001), and HDL-C increased 18.6% and 9.7% (treatment difference 8.8%, p<0.001) in the combination group versus monotherapy group, respectively. No drug-related serious adverse experiences were observed. No cases of clinical myopathy or severe abnormalities in liver function were reported.

The lipid arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was a randomized, double-blind, multicenter study of 5,518 patients with type 2 diabetes.[259] After 1 month of open-label simvastatin, patients were randomized to simvastatin plus fenofibrate 160 mg daily or simvastatin plus placebo. The mean age was 62 years, 31% were women, 37% had a prior CV event, mean systolic blood pressure was 134 mm Hg, mean HbA1c was 8.1%, and about 60% were taking a statin prior to enrollment. In the fenofibrate group, LDL-C decreased from 100 to 81 mg/dL, HDL-C increased from 38 to 41.2 mg/dL, and TG decreased from 189 to 147 mg/dL. In the placebo group, LDL-C decreased from 101 to 80 mg/dL (p=0.16 between groups), HDL-C increased from 38 to 40.5 mg/dL (p=0.01 between groups), and TG decreased from 186 to 170 mg/dL (p<0.001 between groups). After a mean follow-up of 4.7 years, the annual rate of the primary outcome (first occurrence of nonfatal MI, nonfatal stroke, or death from CV causes) was 2.2% with fenofibrate versus 2.4% with placebo (HR in the fenofibrate group, 0.92; 95% CI, 0.79 to 1.08; p=0.32). There were also no significant differences between the 2 study groups with respect to any secondary outcome. Hazard ratios for the secondary outcomes, including the individual components of the primary outcome, ranged from 0.82 to 1.17 (p≥0.1 for all comparisons). Annual rates of death were 1.5% in the fenofibrate group and 1.6% in the placebo group (HR, 0.91; 95% CI, 0.75 to 1.1; p=0.33). In subgroup analysis, men appeared to benefit, while women appeared to be harmed from fenofibrate therapy (p for interaction=0.01). Also, a high TG (≥203 mg/dL)/low HDL-C (≤35 mg/dL) profile appeared to non-significantly benefit (p for interaction=0.057) the fenofibrate group versus placebo. Study drug was discontinued due to a decrease in estimated glomerular filtration rate in 2.4% in the fenofibrate group and 1.1% of placebo. Serum creatinine levels increased in the fenofibrate group soon after randomization but then remained constant, compared with placebo. There was no evidence of increased risk of myositis or rhabdomyolysis in the fenofibrate/simvastatin group. The trial was sponsored by the National Heart, Lung, and Blood Institute (NHLBI).

fenofibric acid (Trilipix)

In 3, 12-week, randomized, double-blind, multicenter studies of 2,698 patients with mixed dyslipidemia, efficacy and safety of fenofibric acid in combination with statins to each single agent were reviewed.[260] Moderate doses of rosuvastatin (Crestor®) 10 mg or 20 mg, simvastatin 20 mg or 40 mg, or atorvastatin (Lipitor®) 20 mg or 40 mg were co-administered with 135 mg of fenofibric acid. In the pooled analysis, combination therapy with a low-dose and a moderate-dose statin significantly

increased HDL-C (18.1% and 17.5%, respectively) and decreased TG (43.9% and 42%, respectively) compared to the corresponding dose of statin monotherapy (7.4% and 8.7% for HDL-C, -16.8% and -23.7% for TG; p<0.001 for all comparisons). In addition, both doses of combination therapy resulted in mean percent decreases (33.1% and 34.6%, respectively) in LDL-C that is significantly greater than fenofibric acid monotherapy (5.1%, p<0.001).

gemfibrozil

The Helsinki Heart Study, a randomized, double-blind primary prevention study, found that gemfibrozil 1,200 mg/day was associated with a significant reduction in total plasma TG and a significant increase in HDL-C in men aged 40 to 55 years old (n=4,081) compared to placebo.[261,262] Over the 5-year study period, there was a 34% relative risk reduction (p<0.02) in the incidence of cardiac endpoints (MI and cardiac death) with the use of gemfibrozil compared to placebo.[263] At the conclusion of the study, all participants were given the opportunity to receive gemfibrozil for an additional 3.5 years.[264] After the additional open-label period, there was no significant difference in CV or all-cause mortality between the 2 groups.

During screening for the Helsinki Heart Study, approximately 600 dyslipidemic individuals were detected who exhibited signs and symptoms of possible CHD; these subjects were excluded from the primary study.[265] Three-hundred and eleven of these patients were randomized to receive gemfibrozil 1,200 mg/day and 317 subjects to receive placebo over 5 years in double-blind fashion. The primary endpoint, a composite of fatal and non-fatal MI and cardiac deaths, did not differ significantly between the placebo and gemfibrozil groups. The same was true for total mortality. In the study, data were not evaluated for several key prognostic factors, including the presence, and between group distribution, of the true prevalence of CHD, extent of coronary artery obstructions, and degree of left ventricular dysfunction.

A 13-year post trial follow-up of the Helsinki Heart Study compared CHD, cancer, and all-cause mortality among the original gemfibrozil and original placebo groups. Gemfibrozil had a 23% relative risk reduction of CHD mortality compared to placebo (p=0.05).[266]

In the double-blind Veterans' Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) study, 2,531 men with CHD, mean HDL-C of 31.5 mg/dL and mean LDL-C of 111 mg/dL, were randomized to gemfibrozil 1,200 mg/day or placebo.[267] The primary study outcome was nonfatal MI or death from coronary causes. At 1 year, the mean total-C was 4% lower, HDL-C was 6% higher, and TG was 31% lower in the active treatment than the placebo group; there was no between group difference in LDL-C. After a median follow-up of 5.1 years, a primary event occurred in 17.3% of patients in the gemfibrozil group and 21.7% of patients in the placebo group, a significant relative risk reduction of 22% (95% CI, 7 to 35%; p=0.006). There was also a 24% relative risk reduction in the secondary composite endpoint of death from CHD, nonfatal MI, and stroke (p<0.001 compared to placebo). There were no significant differences between groups in the incidences of coronary revascularization, hospitalization for unstable angina, death from any cause, and cancer. Subsequent predefined subanalyses showed a reduced incidence in the primary outcome in patients with chronic renal insufficiency (25% relative risk reduction; p=0.02) and in patients with diabetes (32% relative risk reduction; p=0.004).[268,269]

icosapent ethyl (Vascepa)

MARINE: In a randomized, double-blind, multicenter, placebo-controlled study, 229 patients with severe hypertriglyceridemia (baseline TG levels 500 to 2,000 mg/dL) with or without background statin therapy were randomized to icosapent ethyl 4 grams daily, icosapent ethyl 2 grams daily, or placebo for 12 weeks.[270] Median TG level was 680 mg/dL, 657 mg/dL and 703 mg/dL in the 4-gram, 2-gram and placebo groups, respectively. The primary endpoint was placebo-corrected median percent change in TG from baseline to week 12. Icosapent ethyl resulted in a 33.1% reduction in the 4-gram group ($p<0.001$ versus placebo) and a 19.7% reduction in the 2-gram group ($p=0.0051$). LDL-C was not significantly increased in either group. The study found that patients with a higher baseline TG level demonstrated larger reductions. In those with a baseline TG > 750 mg/dL, the 4 gram dosage resulted in a 45.4% reduction (n=28, $p=0.0001$) and the 2 gram dosage resulted in a 32.9% reduction (n=28, $p=0.0016$). Patients who were on concomitant statin therapy had a larger decrease in TG compared to those not treated with statins (4-gram group on statins 65% reduction, $p=0.0001$; 2-gram group on statins 40.7% reduction, $p=0.0276$ compared to 4-gram group no statin 25.8% reduction, $p=0.0002$; 2-gram group no statins 16.4%, $p=0.036$). Safety profile of icosapent ethyl was similar to placebo.

ANCHOR: The efficacy and safety of icosapent ethyl were evaluated in a phase 3, double-blind, 12-week trial in high-risk statin-treated patients with residually high TG levels (≥ 200 and less than 500 mg/dL) despite LDL-C control (≥ 40 mg/dL and < 100 mg/dL).[271] Patients (n = 702) on a stable diet were randomized to icosapent ethyl 4 g or 2 g per day or placebo. The primary endpoint was median percent change in TG levels from baseline versus placebo. Both doses of icosapent ethyl significantly decreased TG levels by 21.5% ($p<0.0001$) and 10.1% ($p=0.0005$), respectively, and non-HDL-C by 13.6% ($p<0.0001$) and 5.5% ($p=0.0054$), respectively. Icosapent ethyl 4 g/day produced greater TG and non-HDL cholesterol decreases in patients with higher-efficacy statin regimens and greater TG decreases in patients with higher baseline TG levels. Icosapent ethyl 4 g/day also decreased LDL-C, apo B, total cholesterol, VLDL-C, lipoprotein-associated phospholipase A(2), and high-sensitivity C-reactive protein compared to placebo ($p<0.001$ for all comparisons). Icosapent ethyl was generally well tolerated, with safety profiles similar to placebo.

lomitapide (Juxtapid)

The safety and effectiveness of lomitapide (as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available) were evaluated in a single-arm, open-label trial involving 29 adults with HoFH.[272] Current lipid-lowering therapy was maintained. Patients were counseled to follow a low-fat diet (< 20% calories from fat) and to take dietary supplements. Sixty-two percent of patients were receiving apheresis. Lomitapide dose was titrated based on safety and tolerability from 5 mg to a maximum of 60 mg daily. The primary endpoint was mean percent change in LDL-C measured at week 26. Patients remained on lomitapide for an additional year to assess long-term safety. At week 26, LDL-C was reduced by 50% (95% CI, -62 to -39; $p<0.0001$) from baseline; LDL-C levels remained reduced by 44% (95% CI, -57 to -31; $p<0.0001$) at week 56 and 38% (95% CI, -52 to -24; $p<0.0001$) at week 78. The most common adverse events reported were gastrointestinal symptoms. Four patients had aminotransaminase levels of more than 5 times the upper limit of normal, which resolved after dose reduction or temporary interruption of lomitapide.

mipomersen (Kynamro)

A 26-week, double-blind, phase 3 study in patients aged 12 years and older with clinical diagnosis or genetic confirmation of HoFH, who were already receiving the maximum tolerated dose of a lipid-lowering drug, were randomly assigned to mipomersen (n=34) 200 mg subcutaneously weekly or placebo (n=17).[273] The mean age was 32 years. The primary endpoint was percentage change in LDL-C from baseline. The mean percent reduction of LDL-C was significantly greater with mipomersen (24.7%; 95% CI, -31.6 to -17.7) than placebo (3.3%; 95% CI, -12.1 to +5.5; p=0.0003). The most common adverse events were injection-site reactions, reported in 76% of patients in mipomersen group compared to 24% in the placebo group. Twelve percent of patients on mipomersen and none on placebo had increases in alanine aminotransferase levels of 3 times or more the upper limit of normal.

niacin IR

The Coronary Drug Project was a 9-year, double-blind study conducted by the National Heart, Lung, and Blood Institute (NHLBI) to assess the long-term efficacy and safety of several lipid-influencing drugs (conjugated estrogens 2.5 mg or 5 mg/day, clofibrate 1.8 gm/day, dextrothyroxine 6 mg/day, niacin 3 gm/day, or placebo) in 8,341 men aged 30 to 64 years with documented MI.[274] The 2 estrogen regimens and dextrothyroxine were discontinued early because of adverse effects. No evidence of efficacy was found for the clofibrate treatment. Niacin treatment showed modest benefit in decreasing nonfatal recurrent MI but did not decrease total mortality. After a mean follow-up of 15 years, mortality from all causes in each of the drug groups, except for niacin, was similar to that in the placebo group. Study authors state that a late benefit of niacin occurred after discontinuation of the drug that may be a result of a translation into a mortality benefit over subsequent years of the early favorable effect of niacin in decreasing nonfatal recurrent MI or a result of the cholesterol-lowering effect of niacin, or both. Mortality in the niacin group was 11% lower than in the placebo group (52% versus 58.2%; p=0.0004).

niacin ER (Niaspan)

In a double-blind, randomized, placebo-controlled trial, niacin ER 1,000 mg daily (n = 87) or placebo (n=80) were added to statin therapy in 167 patients with CAD and low HDL-C (< 45 mg/dL).[275] Patients were initially started on niacin ER 500 mg and then titrated to 1,000 mg daily after 1 month. A total of 149 patients completed the study. Baseline carotid intima-media thickness (CIMT), LDL-C (mean 89 mg/dL), and HDL-C (mean 40 mg/dL) were comparable in the 2 groups. After 12 months, HDL-C increased by 21% in the niacin group. The mean CIMT increased significantly in the placebo group (p<0.001) but was unchanged in the niacin group. The difference in the CIMT progression was not statistically significant (p=0.08); however, niacin significantly reduced the rate of IMT progression in patients without insulin resistance (p=0.026). Cardiovascular event rates were similar in the small trial (3.8% in the niacin group and 9.6% in the statin-only group; p=0.2).

omega-3-acid ethyl esters (Lovaza)/simvastatin versus simvastatin

A randomized, double-blind, placebo-controlled, parallel group trial compared the combination of omega-3 acid ethyl esters 4 gm daily and simvastatin 40 mg per day with simvastatin 40 mg per day monotherapy in 254 patients with persistent high TG (200 to 499 mg/dL).[276,277] Patients were treated with 8 weeks of open-label simvastatin 40 mg daily prior to randomization to reduce LDL-C to no

greater than 10% above NCEP ATP III goal and remained on this dose throughout the study. After the initial open-label phase, patients were then randomized to either omega-3-acid ethyl esters or placebo for an additional 8 weeks. Combination therapy versus monotherapy resulted in a median percentage change in TG of -29.5% versus -6.3%, respectively, (p<0.0001). The mean percentage change in HDL-C was +3.4% for combination therapy versus -1.2% for monotherapy, (p<0.05). The mean percentage change in LDL-C was +0.7% for the combination group and -2.8% for monotherapy (p=0.05).

A 16-week study randomized patients with elevated non-HDL-C greater than160 mg/dL and TG ≥250 mg/dL, and ≤599 mg/dL levels to double-blind treatment with prescription omega-3-acid ethyl esters, 4 g/day, or placebo.[278] Patients also received escalating dosages of open-label atorvastatin (weeks 0-8, 10 mg/day; weeks 9-12, 20 mg/day; weeks 13-16, 40 mg/day). Omega-3-acid ethyl esters plus atorvastatin 10, 20, and 40 mg/day reduced median non-HDL-C levels by 40.2% versus 33.7% (p<0.001), 46.9% versus 39% (p<0.001), and 50.4% versus 46.3% (p<0.001) compared with placebo plus the same doses of atorvastatin at the end of 8, 12, and 16 weeks, respectively. Omega-3-acid ethyl esters plus atorvastatin also reduced median TC, TG, and LDL-C levels and increased HDL-C levels to a significantly greater proportion compared to placebo plus atorvastatin. At study end, percent changes from baseline LDL-C, apolipoprotein A-I, and apolipoprotein B levels were not significantly different between groups.

alirocumab (Praluent) versus placebo

ODYSSEY COMBO I was a multicenter, phase 3, randomized, double-blind, 52-week trial that evaluated the effect of alirocumab in patients with a history of atherosclerotic cardiovascular disease (ASCVD) not at goal (LDL-C ≥ 70 mg/dL) or moderate chronic kidney disease (CKD) or diabetes with additional risk factors not at goal (LDL-C ≥ 100 mg/dL) despite maximally tolerated statin with or without other lipid-lowering therapy.[279] Patients with known HeFH or HoFH were excluded. Overall, 209 patients were randomized (2:1) to subcutaneous (SC) alirocumab and 107 to placebo. Eighty four percent had clinical ASCVD. Patients in the alirocumab group were initiated at a dose of 75 mg every 2 weeks with possible up-titration to 150 mg every 2 weeks at week 12 in patients whose LDL-C was still ≥ 70 mg/dL. After 24 weeks, the treatment difference between alirocumab and placebo in mean LDL-C percent change was 45.9% (p<0.0001). The treatment difference between alirocumab and placebo for percent change from baseline in Apo B, Non-HDL-C, total cholesterol, and triglyceride reductions, and HDL increase at 24 weeks were 35.8%, 37.5%, 25%, 0.6%, and 7.3%, respectively (p<0.0001 except all for triglycerides). The dose was up-titrated to 150 mg in 16% of patients treated with alirocumab for at least 12 weeks.

ODYSSEY FH I and II were both 78-week multicenter, multinational, randomized, double-blind, placebo-controlled trials in patients with HeFH not at goal (LDL-C ≥ 70 mg/dL if patient had prior CVD and ≥ 100 mg/dL if no history of CVD) despite maximally tolerated statin with or without other lipid lowering therapy.[280,281] Overall, 490 patients were assigned to alirocumab and 245 to placebo. Patients in the alirocumab group were initiated at a dose of 75 mg every 2 weeks with possible up-titration to 150 mg every 2 weeks at week 12 in patients whose LDL-C was still ≥ 70 mg/dL. After 24 weeks, the treatment difference between alirocumab and placebo in mean LDL-C percent change was 57.9% (p<0.0001) and 51.4% (p<0.0001) in FH I and II, respectively. In FH I, the treatment difference between alirocumab and placebo for percent change from baseline in Apo B, Non-HDL-C, total cholesterol, and triglyceride reductions, and HDL increase at 24 weeks were 45.8%, 52.4%, 38.7%, 16%, and 8%, respectively (p<0.0001 for all). In FH II, the treatment differences were 39.3%, 45.7%, 32.8%, 10.9%,

and 6.8%, respectively (p<0.01 for all). The dose was up-titrated to 150 mg in 43.4% and 38.6% of patients treated with alirocumab for at least 12 weeks in FH I and II, respectively.

ODYSSEY High FH, with a nearly identical trial design to FH I and II, was a 78-week trial in patients with HeFH and a baseline LDL-C ≥ 160 mg/dL. Overall, 72 patients were assigned to alirocumab 150 mg every 2 weeks and 35 to placebo.[282,283,284] After 24 weeks, the treatment difference between alirocumab and placebo in mean LDL-C percent change was 39.1% (p<0.0001). The treatment difference between alirocumab and placebo for percent change from baseline in apo B, non-HDL-C, total cholesterol, and triglyceride reductions, and HDL increase at 24 weeks were 30.3%, 35.5%, 28.4%, 8.7%, and 3.7%, respectively (p<0.001 for all except triglycerides and HDL).

ODYSSEY LONG TERM, a multinational, phase 3, randomized, double-blind, placebo-controlled, 18-month trial, evaluated the effect of alirocumab in non-familial hypercholesterolemia (non-FH) and HeFH ASCVD patients with high or very high cardiovascular risk not at goal (LDL-C ≥ 70 mg/dL).[285] Overall, 1,553 patients were assigned to alirocumab 150 mg every 2 weeks and 788 to placebo. Sixty-nine percent were non-FH patients with clinical ASCVD and 18% had HeFH. After 24 weeks, the treatment difference between alirocumab and placebo in mean LDL-C percent change was 61.9% (95% CI, -64.3 to -59.4; p<0.0001). The treatment difference between alirocumab and placebo for percent change from baseline in Apo B, Non-HDL-C, total cholesterol, and triglyceride reductions, and HDL increase at 24 weeks were 54%, 52.3%, 37.5%, 17.3%, and 4.6%, respectively (p<0.0001).

alirocumab (Praluent) versus ezetimibe (Zetia)

The ODYSSEY COMBO II trial followed an identical study design as COMBO I but included an active comparator rather than placebo. It was a 104-week, double-blind, double-dummy, active-controlled, parallel-group, phase 3 study, compared alirocumab to ezetimibe (n=720) in high-risk patients with ASCVD and elevated LDL-C despite maximal statin treatment (n=720).[286] Patients with known He-FH or Ho-FH were excluded. Patients were randomized to SC alirocumab 75 mg every 2 weeks or oral ezetimibe 10 mg daily, both with background statin therapy. After 24 weeks, the treatment difference between alirocumab and ezetimibe in mean LDL-C percent change was 29.8% (95% CI, -34.4 to -25.3; p<0.0001) favoring alirocumab, the primary endpoint. Secondary endpoints included percent change in LDL-C at week 12 and 52, proportion of patients reaching calculated LDL-C less than 70 mmol/L at week 24, and percent change in apolipoprotein B, non-HDL-C, total cholesterol, lipoprotein A, HDL-C, fasting triglycerides, and apolipoprotein A-1 from baseline to week 24. Nearly all secondary endpoints also demonstrated superiority of alirocumab compared to ezetimibe (p<0.0001 for all endpoints excluding triglycerides).

The ODYSSEY MONO trial, a phase 3, randomized, double-blind, double-dummy study, compared alirocumab and ezetimibe in 103 moderate risk ASCVD patients that were not on any other background lipid-lowering therapy.[287] Patients with known He-FH or Ho-FH were excluded. Patients were randomized to alirocumab 75 mg SC every 2 weeks (dose could be uptitrated to 150 mg if LDL-C was ≥ 70 mg/dL at week 12) or oral ezetimibe 10 mg daily. Fourteen of the 52 patients in the alirocumab treatment arm were uptitrated at 12 weeks. After 24 weeks, the treatment difference between alirocumab and ezetimibe in mean LDL-C percent change was 31.6% (95% CI, -40.2 to -23; p<0.0001).

The ODYSSEY OPTIONS I study, a phase 3, 24-week, multicenter, randomized, double-blind, active-comparator studies, explored the efficacy of alirocumab in 355 HeFH and non-FH ASCVD patients at high or very high cardiovascular risk not adequately controlled on atorvastatin 20 to 40 mg.[288] Patients were randomized to add-on alirocumab 75 mg SC every 2 weeks (up titration to 150 mg was possible

based on LDL-C level and CV risk at week 12), add-on ezetimibe 10 mg/day, doubled atorvastatin dose, or a switch to rosuvastatin 40 mg (those on atorvastatin 40 mg/day only). At 24 weeks in the patient group treated with 20 mg atorvastatin at baseline, the least squares (LS) mean (standard error [SE]) percent change in LDL-C from baseline in the add-on alirocumab group was -44.1% (±4.5%), -20.5% (±4.7%) in the ezetimibe group, and -5% (±4.6%) in the atorvastatin dose doubling group (p=0.0004 alirocumab versus ezetimibe; p<0.0001 alirocumab versus atorvastatin). At 24 weeks in the patient group treated with atorvastatin 40 mg at baseline, the LS mean (SE) percent change in LDL-C from baseline was -54% (±4.3%) in the add-on alirocumab group, -22.6% (±4.3%) in the ezetimibe group, -4.8% (±4.2%) in the atorvastatin dose doubling group, and -21.4% (±4.2%) in the rosuvastatin group (p<0.0001 for all comparisons).

evolocumab (Repatha) versus placebo

DESCARTES, a 52-week, phase 3, multinational, randomized, double-blind trial, evaluated the effect of evolocumab 420 mg once monthly compared to placebo (2:1) in patients 18 to 75 years of age with hyperlipidemia, an LDL cholesterol level of 75 mg/dL or higher, and a fasting triglyceride level of 400 mg/dL or lower who were stabilized on either diet alone, 10 mg of atorvastatin, 80 mg of atorvastatin, or 80 mg of atorvastatin plus ezetimibe (n=901).[289] The difference in least-squares mean reduction in LDL-C from baseline for evolocumab compared to placebo was 57% (SE, ±2.1; p<0.001) compared to placebo at 52 weeks. The treatment difference between evolocumab and placebo for percent change from baseline in Apo B, non-HDL-C, and triglycerides at 12 weeks were -44.2%, -50.3%, and -11.5%

RUTHERFORD-2, a 12-week, multicenter, randomized, double-blind, placebo-controlled trial, evaluated the safety and efficacy of evolocumab in 329 patients with HeFH. Evolocumab (dosed either 140 mg every 2 weeks or 420 mg once monthly) was compared to placebo in patients aged 18 to 80 years who had a baseline LDL-C ≥ 100 mg/dL and were on a stable on statins with or without other lipid-lowering therapies.[290] Compared with placebo, evolocumab twice monthly and once monthly reduced LDL-C by -59.2% (95% CI, -65.1 to -53.4; p<0.001) and 61.3% (95% CI, -69 to -53.6; p<0.001), respectively, at 12 weeks. The treatment difference between evolocumab and placebo for percent change from baseline in Apo B, non-HDL-C, and triglycerides at 12 weeks were -49.1%, -54.8%, and -19.6% in the every 2 week group and -49.4%, -55%, and -11.6% in the once monthly group, respectively (all p < 0.0001 excluding triglycerides in the monthly treatment group [p=0.0214]).

TESLA (Part B), a 12-week, phase 3, multinational, randomized, double-blind, placebo-controlled trial, evaluated the efficacy of evolocumab in 49 patients with HoFH.[291] Patients aged 13 to 80 years who had a baseline LDL-C ≥ 130 mg/dL and were on lipid-lowering therapies, but not on lipid-apheresis therapy, were randomized 2:1 to evolocumab 420 mg once monthly or placebo. Compared with placebo, evolocumab reduced LDL-C by 30.9% (95% CI, -43.9 to -18; p<0.0001) at 12 weeks. The treatment difference between evolocumab and placebo for percent change from baseline in Apo B, HDL-C, and triglycerides were -23.1%, -0.1%, and 0.3, respectively (p value significant for Apo B only [p=0.0007]).

evolocumab (Repatha) versus ezetimibe (Zetia)

LAPLACE-2, a 12-week, randomized, double-blind trial, evaluated the effect of evolocumab (dosed either 140 mg every 2 weeks or 420 mg once monthly) compared to placebo or ezetimibe 10 mg/day in 1,899 patients with primary hypercholesterolemia and mixed dyslipidemia stabilized on moderate or high-intensity statin therapy.[292] At the mean of 10 and 12 weeks, evolocumab every 2 weeks reduced LDL-C levels by 66% (95% CI, 58% to 73%) to 75% (95% CI, 65% to 84%) and monthly by 63% (95% CI, 54% to 71%) to 75% (95% CI, 67% to 83%) compared to placebo in the moderate and high intensity statin groups. Ezetimibe reduced LDL-C values by 17% to 24% from baseline, evolocumab (every 2 weeks) reduced LDL-C values by 61% to 62% ($p<0.001$ versus ezetimibe), and evolocumab (monthly) reduced LDL-C values by 62% to 65% ($p<0.001$ versus ezetimibe).

MENDEL-2, a randomized, controlled, phase 3 clinical trial, studied evolocumab (dosed either 140 mg every 2 weeks or 420 mg once monthly) compared to either ezetimibe 10 mg/day or placebo as monotherapy in 614 patients 18 to 80 years of age with primary hypercholesterolemia, fasting LDL-C ≥100 and less than 190 mg/dL, and Framingham risk scores ≤10%.[293] At 12 weeks, average LDL-C decreased by a mean of 57% (95% CI, -59.5% to -54.6%) with evolocumab every 2 weeks, 56.1% (95% CI, -58.3% to -53.9%) with evolocumab once monthly, 0.1% to 1.3% (95% CI, -3.2% to 3.4%; and 95% CI, -4.4% to 1.7%, respectively) in placebo groups 1 and 2, and 17.8% to 18.6% (95% CI, -21% to -14.5%; and 95% CI, -21.6% to -15.5%, respectively) in ezetimibe groups 1 and 2 ($p<0.001$ evolocumab versus placebo and ezetimibe). These reductions were also significant for the mean of week 10 and week 12 compared to placebo and ezetimibe ($p<0.001$), the other co-primary endpoint. Significant differences were found when comparing both dosing schedules of evolocumab to placebo and ezetimibe in the following lipid parameters (apolipoprotein B, lipoprotein a, non-HDL-C, and HDL-C [$p<0.02$ for all comparisons]).

GAUSS-2, a 12-week, double-blind, randomized controlled trial, studied evolocumab (dosed either 140 mg every 2 weeks or 420 mg once monthly) compared to ezetimibe 10 mg/day in 307 patients with hyperlipidemia diagnosed with statin intolerance.[294] The mean percent change in LDL-C from baseline at week 12 was -55.3% to -56.1% with evolocumab and -16.6% to -19.2% with ezetimibe (treatment difference -36.9 to -38.7; $p<0.001$ for both comparisons). The mean percent change in LDL-C from baseline at week 10 and 12 was -52.6% to -56.1% with evolocumab and-15.1% to -18.1% with ezetimibe (treatment difference -37.6 to -38.1; $p<0.001$ for both comparisons). Significant differences were also seen in some secondary endpoints: apolipoprotein B, lipoprotein a, and LDL-C less than 70 mg/dL ($p<0.001$) but not in HDL-C or apolipoprotein A-1.

META-ANALYSES

Fibric acids were compared to niacin in a meta-analysis evaluating lipid parameter effects and risk reductions for major cardiac events.[295] Data from 53 trials (n=16,802) using fibric acids and 30 trials (n=4,749) using niacin were included in the meta-analysis. Fibric acids included agents which have never been available in the U.S., in addition to gemfibrozil and fenofibrate. Niacin products included immediate-, sustained-, and extended-release formulations. Reductions in LDL-C and TG were 36% and 8% for fibric acids and 20% and 14% for niacin, respectively. Increases in HDL-C were 10% and 16% for fibric acids and niacin, respectively. Relative risk reduction for major cardiac events was 25% and 27% for fibric acids and niacin, respectively.

A systematic review searched the literature to identify randomized, double-blind, placebo-controlled trials examining the effect of fibrates on lipid profiles or cardiovascular outcomes.[296] Fibrates were associated with greater reductions in total cholesterol (range: -101.3 mg/dL to -5 mg/dL) and TG (range: -321.3 mg/dL to -20.8 mg/dL), and a greater increase in HCL-C (range: +1.1 mg/dL to +17.9 mg/dL), compared to placebo, in all trials. Although not consistently, fibrates tended to be associated with a greater reduction in LCL-C (range: -76.3 mg/dL to +38.7 mg/dL) than placebo. Fibrates were better than placebo at preventing nonfatal MI (OR=0.78; 95% CI, 0.69-0.89), but not all-cause mortality (OR=1.05; 95% CI, 0.95-1.15).

A systematic review and meta-analysis searched for prospective randomized placebo-controlled fibrate trials with effect on CV outcomes published between 1950 and March 2010.[297] Medline, Embase, and the Cochrane Library were searched. Summary estimates of relative risk (RR) reductions were calculated with a random effects model. Outcomes analyzed included major CV events, coronary events, stroke, HF, coronary revascularization, all-cause mortality, CV death, non-vascular death, sudden death, new onset albuminuria, and drug-related adverse events. Eighteen trials with 45,058 patients were identified, including 2,870 major CV events, 4,552 coronary events, and 3,880 deaths. Fibrate therapy produced a 10% RR reduction (95% CI, 0 to 18) for major CV events (p=0.048) and a 13% RR reduction (95% CI, 7 to 19) for coronary events (p<0.0001), but had no benefit on stroke (−3%; 95% CI, −16 to 9; p=0.69). There was no effect of fibrate therapy on the risk of all-cause mortality (0%; 95% CI, −8 to 7; p=0.92), CV mortality (3%; 95% CI, −7 to 12; p=0.59), sudden death (11%; 95% CI, −6 to 26; p=0.19), or non-vascular mortality (−10%; 95% CI, −21 to 0.5; p=0.063). Fibrates reduced the risk of albuminuria progression by 14% (95% CI, 2 to 25; p=0.028). Serious drug-related adverse events were not significantly increased by fibrates (RR 1.21; 95% CI, 0.91 to 1.61; p=0.19), although increases in serum creatinine concentrations were common (1.99; 95% CI, 1.46 to 2.7; p<0.0001).

A meta-analysis of 11 randomized trials with 6,616 patients found niacin significantly reduced major coronary events (relative OR, 25%; 95% CI, 13 to 35), stroke (25%; 95% CI, 8 to 41), and any CV events (27%; 95% CI, 15 to 37).[298] In comparison with the non-niacin group, more patients in the niacin group showed regression of coronary atherosclerosis (relative increase 92%; 95% CI, 39 to 67), but the rate of patients with progression decreased by 41% (95% CI, 25 to 53). Similar effects of niacin were found on carotid intima thickness with a weighted mean difference in annual change of -17 microm/year (95% CI, -22 to -12).

Effects on Lipids for Selected Agents[299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315]

While outcomes data are lacking for many of the non-statin lipotropics, the effects of these agents on the lipid profile are well documented and may serve as an indirect indicator of the efficacy. Conditions and populations in clinical trials may vary.[316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344]

Drug	total-C (% change)	LDL-C (% change)	HDL-C (% change)	TG (% change)
Bile Acid Sequestrants cholestyramine, colestipol (Colestid), colesevelam (Welchol)	-9 to -13	-12 to -30	+3 to +9	0 to +25
Cholesterol Absorption Inhibitors ezetimibe (Zetia)	-12 to -14	-13 to -20	+1 to +5	-5 to -11
Fibric Acids fenofibrate (Antara, Fenoglide, Lipofen, Tricor, Triglide) gemfibrozil (Lopid)	-4 to -26	-27 to +9	+ 6 to +18	- 29 to -54
fenofibric acid (Fibricor)	-9 to -22	-31 to +45	+10 to +23	- 24 to -54
fenofibric acid (Trilipix)	-12	-5	+16	-31
lomitapide (Juxtapid)	-36	-40	-7	-45
mipomersen (Kynamro)	-21	-25	+15	-18
niacin ER (Niaspan)	-3 to -10	-14 to +2	+18 to +26	-13 to -29
niacin IR (Niacor)	-10 to -20	-10 to -20	+20 to +35	-30 to -70
omega-3-acid ethyl esters (Lovaza)	-10	+45	+9	-45
icosapent ethyl (Vascepa)	-7	-5	-4	-27
alirocumab (Praluent)	-27 to -38	-43 to -61	+4 to +9	-6 to -16
evolocumab (Repatha)	-17 to -42	-22 to -65	+4 to +9	-5 to -20

SUMMARY

The preponderance of outcomes data supports the use of statins as the primary agents for LDL-C reduction therapy and for primary and secondary prevention of coronary heart disease (CHD). According to the 2013 ACC/AHA practice guidelines for the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, non-statin therapies do not provide acceptable ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD. However, ACC/AHA recognizes that maximal statin therapy might not be adequate to lower LDL–C sufficiently to reduce ASCVD event risk in individuals with primary severe elevations of LDL–C at which time the addition of non-statin agents can be considered. This guideline focuses on treatments proven to reduce ASCVD events and is not intended to be a comprehensive approach to lipid management. They suggest examination of treatment of hypertriglyceridemia and use of non-HDL-C Apo B, Lp(a), or LDL particles in guiding treatment decisions.

The 2012 Endocrine Society guideline on the evaluation and treatment of hypertriglyceridemia recommends drug therapy to reduce the risk of pancreatitis in patients with severe and very severe hypertriglyceridemia; a fibrate is considered a first-line treatment. For patients with moderate to severe hypertriglyceridemia, fibrates, niacin, and omega-3 fatty acids alone or in combination with statins may be considered. Statins should not be used alone for severe or very severe

hypertriglyceridemia; however, statins may be useful for the treatment of moderate hypertriglyceridemia to modify CVD risk.

The bile acid sequestrant, cholestyramine, has been shown to reduce major coronary events and CHD deaths. The bile acid sequestrants are effective in lowering LDL-C and a small increase in HDL-C. Effect on decrease in TG levels has been reported between 0 and 25%. They can be used in combination with statins. Patients generally have poor compliance to bile acid sequestrants because of the side effect profile. Colesevelam (WelChol) provides an alternative to cholestyramine and colestipol with a potential lower incidence of GI effects. Colesevelam has also been studied in pediatrics ages 10 to 17 years of age with heterozygous familial hypercholesterolemia. In patients with type 2 diabetes mellitus, colesevelam only provides modest HbA1c reductions (-0.5%) and can provide an option in patients who are almost at HbA1c goal who also require lipid lowering.

Gemfibrozil (Lopid) has demonstrated reductions in risk of CHD primarily in subsets of patients with high TG, low HDL-C, and characteristics of metabolic syndrome. In the FIELD study in patients with type 2 diabetes mellitus, fenofibrate was not shown to reduce CHD disease morbidity and mortality. Fenofibrate produced a nonsignificant reduction in the primary endpoint of coronary events. Non-fatal MI and total CV events were significantly reduced, but all-cause mortality was not. In the ACCORD trial, combination of fenofibrate and simvastatin did not reduce rates of CV disease, compared to simvastatin monotherapy. The ACCORD findings do not support the routine use of combination fenofibrate and statin therapy, over statin therapy alone, to reduce CV risk in most patients with type 2 diabetes that are at high risk for CV disease. Fibric acids lower TG levels and raise HDL-C levels to a greater extent than do the statins, but fibrates as a group have less favorable effects on clinical CV outcomes. Depending on the specific type of dyslipidemia, the fibric acids may lower total-C and LDL-C, although not as significantly as the statins. The fibric acids should be considered as an alternative agent to the statins for specific lipid disorders or can be used as add-on therapy with caution considering the increased risk of rhabdomyolysis. Fenofibrate is less likely to interact with statins compared to gemfibrozil. The FDA has removed the indication of fenofibric acid (Trilipix) use in combination with a statin; however, the use of fibrates with statins is still common in practice.

Niacin has been shown to reduce major coronary events. Compared to immediate-release niacin (Niacor), niacin ER (Niaspan) may increase compliance and reduce the incidence of flushing. In the AIM-HIGH study, there was no incremental benefit on CV risk reduction (including myocardial infarctions and stroke) when niacin ER was added to simvastatin therapy versus simvastatin therapy alone. In addition, a small, unexplained, increase in the rate of ischemic stroke was observed in the simvastatin plus extended-release niacin arm compared to simvastatin alone. The FDA has removed the indication for niacin ER (Niaspan) in combination with simvastatin or lovastatin. OTC preparations of niacin are not federally regulated, therefore may lack nicotinic acid or be associated with an increased risk of hepatotoxicity.

Ezetimibe (Zetia) is the only available cholesterol absorption inhibitor. It inhibits intestinal absorption of both dietary and biliary cholesterol by blocking its transport at the brush border of the small intestine. Ezetimibe reduces LDL-C, both when given alone and in combination with a statin. In addition, the IMPROVE-IT study reported lower CV mortality and morbidity when ezetimibe was added to statin (simvastatin) therapy as compared to a statin alone. Ezetimibe has been studied in pediatrics ages 10 to 17 years of age with heterozygous familial hypercholesterolemia.

Lomitapide (Juxtapid) and mipomersen (Kynamro) are approved for use in patients with homozygous familial hypercholesterolemia (HoFH) as an adjunct to a low-fat diet and other lipid-lowering treatments. These agents inhibit the production of apolipoprotein B which leads to a reduction in LDL-C concentration. The safety and effectiveness of lomitapide and mipomersen have not been established in patients with hypercholesterolemia who do not have HoFH.

Omega-3-acid ethyl esters (Lovaza) and icosapent ethyl (Vascepa) reduce TG in patients with very high TG (greater than 500 mg/dL). Although EPA and DHA have shown reduction in major coronary events, the specific formulations for omega-3-acid ethyl esters (Lovaza) and icosapent ethyl (Vascepa) were not used. Several forms of omega-3 fatty acids are sold OTC; however, Lovaza has a high concentration of EPA and DHA in a single capsule. Both twice daily, low capsule count omega-3-acid ethyl esters and icosapent ethyl do not increase the risk of rhabdomyolysis in combination with statins. Icosapent ethyl contains only EPA, while omega-3-acid ethyl esters contain both EPA and DHA.

Alirocumab (Praluent) and evolocumab (Repatha) are recently approved agents in a new class of drugs, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Both have demonstrated significant efficacy in regards to LDL-C lowering, but long-term safety and impact on CV outcomes remain unknown. Current guidelines have not addressed the role of these agents. Use of these agents will depend on the CV risk level of patients and their ability to reach appropriate LDL-C reduction goals with high-intensity statin therapy.

Each class of non-statin lipotropics provides a unique option for use in patients who cannot reach target lipid levels on statin monotherapy or who do not tolerate statins. While there are not outcomes data for each class, their effects on lipids profiles are clearly substantiated.

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